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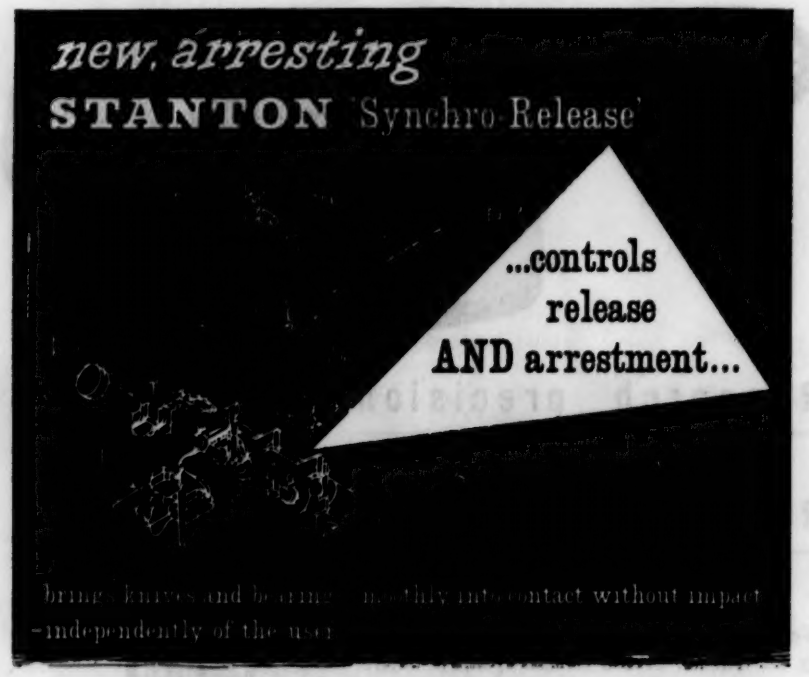

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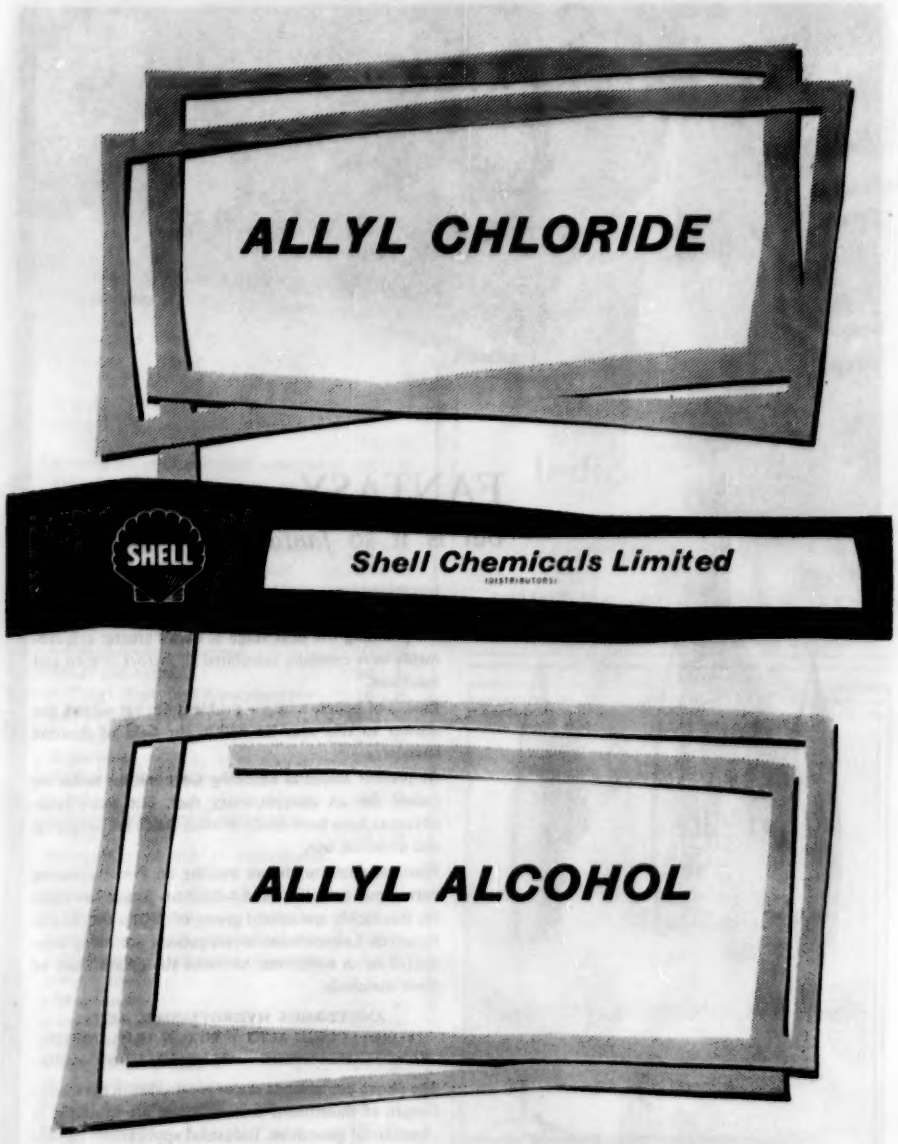

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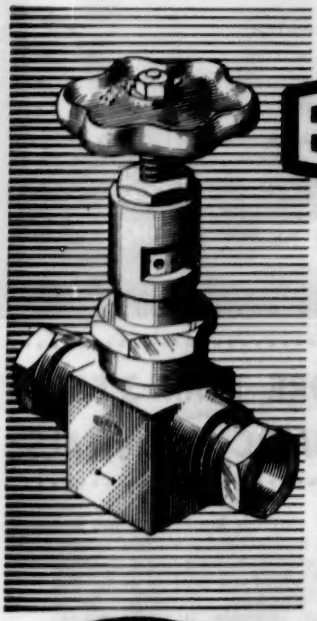

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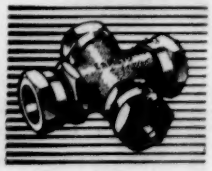

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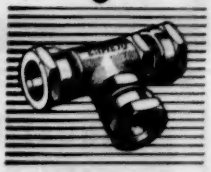

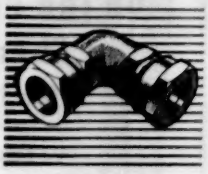

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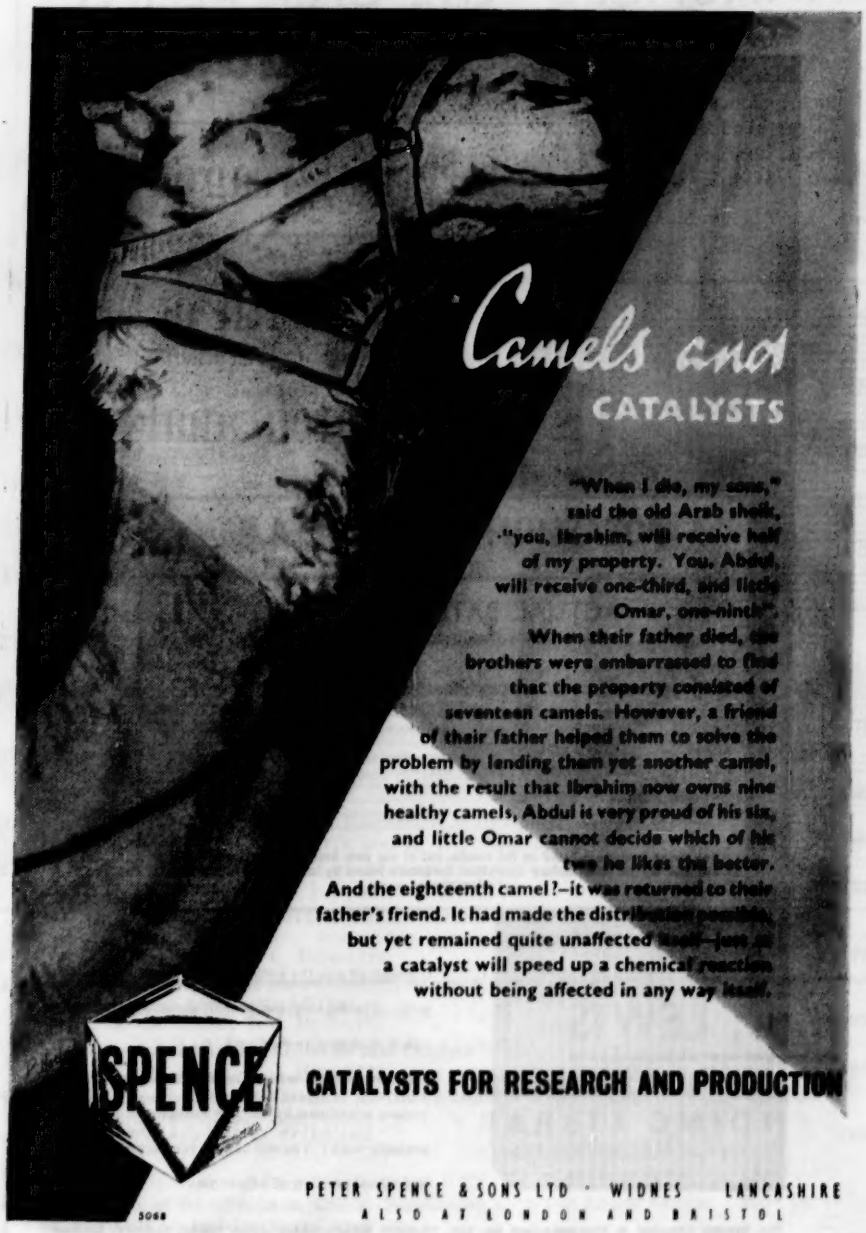
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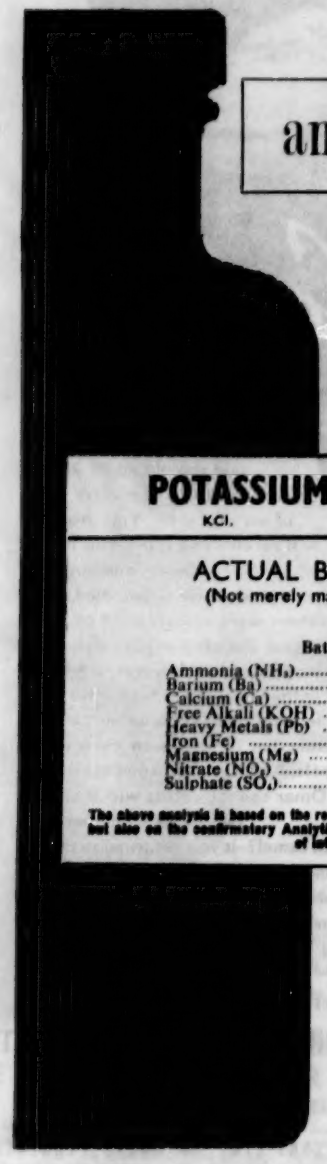

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Heavy Metals (Pb)	0·0003%
Iron (Fe)	0·00008%
Magnesium (Mg)	0·003%
Nitrate (NO_3)	0·0005%
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Molecular Polarisability. The Electro-optical Polarisability Tensor Ellipsoids of Naphthalene, and the α- and β-Fluoro-, -Chloro-, -Bromo-, and -Iodo-naphthalenes.

By (Mrs.) C. G. Le Fèvre and R. J. W. Le Fèvre.

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The molar Kerr constants for the substances named in the title have been measured at infinite dilution in carbon tetrachloride, and the half-axes of the polarisability ellipsoids estimated. While the substitution of an α- or β-hydrogen atom of naphthalene by halogen does not cause the observed value for the *average* polarisability of the resulting halogenonaphthalene to deviate markedly from that expected, yet analysis into b_1, b_2, and b_3 suggests that exaltations and depressions are in fact to be found for the directions collinear with and normal to the C–X bond. The molar Kerr constants of β-halogenonaphthalenes are 2—3 times as large as those of the related α-isomers.

The object of this investigation was, *via* the determination of the electro-optical polarisability ellipsoids of naphthalene and its eight α- and β-halogenated derivatives, to compare the half axes, so found, with those calculated from b_1, b_2, and b_3 for naphthalene in combination with the b_{I}, b_{V}, and b_{T} values for each carbon–halogen bond previously reported by us (*J.*, 1954, 1577).

In order to ascertain the tensor components b_1, b_2, and b_3 for naphthalene, three expressions from different experimental sources are necessary (cf. *J.*, 1953, 4041). For polar molecules in which the orientation of $\mu_{\text{resultant}}$ with reference to the axis of maximum polarisability is known, b_1, b_2, and b_3 may be extracted from the following equations:

$$\frac{3M}{4\pi Nd}\cdot\frac{n_\infty^2-1}{n_\infty^2+2}=\alpha=\frac{b_1+b_2+b_3}{3}\text{ (from the electronic polarisation)} \quad . \quad (a)$$

$$_\infty({}_mK_2)=(4\pi N/9)(\theta_1+\theta_2)$$
$$=\frac{4\pi N}{9}\left\{\frac{1}{45kT}\frac{{}_DP}{{}_EP}[(b_1-b_2)^2+(b_2-b_3)^2+(b_3-b_1)^2]+\right.$$
$$\left.\frac{1}{45k^2T^2}[(b_1-b_2)(\mu_1^2-\mu_2^2)+(b_2-b_3)(\mu_2^2-\mu_3^2)+(b_3-b_1)(\mu_3^2-\mu_1^2)]\right\}$$
(from the molar Kerr constant) . . . . . (*b*)

$$\frac{10\Delta}{6-7\Delta}=\frac{(b_1-b_2)^2+(b_2-b_3)^2+(b_3-b_1)^2}{(b_1+b_2+b_3)^2}$$
(from the depolarisation of scattered light) . . (*c*)

If, however, the molecule is non-polar, then $\theta_2=0$ and equations (*a*) and (*c*) can be combined to give (*b*). Accordingly, for naphthalene, even if a satisfactory figure for the depolarisation factor of scattered light were available, it would be of no help towards elucidating b_1, b_2, and b_3.

The evaluation of the three components for naphthalene by Briegleb (*Z. physikal. Chem.*, 1936, **16**, *B*, 249) by computing expression (*c*) from (*a*) and (*b*) and using the three equations so obtained to solve for b_1, b_2, and b_3 is mathematically unsound, and should therefore be disregarded.

Krishnan (*Indian J. Physics*, 1938, **8**, 431) has estimated b_1, b_2, and b_3 as 26·8, 14·1, and 11·5 $\times$ 10^{-24} respectively. He uses (1) $b_1+b_2+b_3=52{\cdot}42\times10^{-24}$ obtained by adopting 44·37 c.c. as the molecular refractivity;

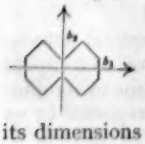
$$(2)\ [(b_1-b_2)^2+(b_2-b_3)^2+(b_3-b_1)^2]/(b_1+b_2+b_3)^2=0{\cdot}145,$$

from the depolarisation factor $\Delta = 0{\cdot}079$ found by Ramakrishna Rao (*ibid.*, 1927, **2**, 84) for naphthalene vapour; and

$$(3)\ (a_1 - a_2)(b_1 - b_2) + (a_2 - a_3)(b_2 - b_3) + (a_3 - a_1)(b_3 - b_1) = 4{\cdot}40 \times 10^{-51}$$

from the Cotton–Mouton effect measurements on molten naphthalene (Salceanu, *Compt. rend.*, 1930, **191**, 486). He calculates $a_1 = -6{\cdot}50$, $a_2 = -7{\cdot}09$, and $a_3 = -30{\cdot}88 \times 10^{-29}$ from the principal susceptibilities of the naphthalene crystal on the basis of the orientations of the two molecules per unit cell described by Banerjee (cf. *Phil. Trans.*, 1933, **231**, 253). We think that, in view of the well-substantiated dimensions of naphthalene (Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 233, 238; Mathieson, Robertson, and Sinclair, *ibid.*, 1950, **3**, 245, 251), a greater similarity in value is to be expected between b_1 and b_2 than between b_2 and b_3; noting also the difficulties of securing accurate depolarisation factors for gases (cf. $\Delta = 0{\cdot}079$ by Ramakrishna Rao or 0·10 by Cabannes, *Compt. rend.*, 1926, **182**, 885), and the variations often to be found among published values for the principal susceptibilities of molecules, it is possible that the *b*'s calculated by Krishnan may not be founded on reliable experimental data.

The b_1 *of Naphthalene.*—*X*-Ray analysis (Robertson, *Proc. Roy. Soc.*, 1933, *A*, **142**, 674) shows that our b_1 for naphthalene always lies in the single crystal along the *c* direction, the refractive index of which is 1·932. Because we have no other information available to us which will give a third equation containing b_1, b_2, and b_3, *faut de mieux* we propose to use Robertson's results to produce an estimate of b_1. The unit cell of naphthalene contains two molecules; its dimensions are $a = 8{\cdot}29$, $b = 5{\cdot}97$, $c = 8{\cdot}68$ Å, and $\beta = 122{\cdot}7°$ (Robertson, *loc. cit.*). The apparent average molecular polarisability in the *c* direction corresponding to $n = 1{\cdot}932$, obtained by means of equation (*a*) and the observed density (1·152 g./c.c.), is $2{\cdot}090 \times 10^{-23}$ c.c. This is not the desired polarisability b_1 since in a crystal lattice subjected to an electric field, each molecular induced dipole induces others in its neighbours. It is necessary for our purpose, therefore, to correct for this secondary induction, and also to convert to a basis of electronic polarisability alone. We shall consider a crystal lattice consisting of eight unit cells, to each of which the naphthalene nucleus O under consideration contributes one eighth of itself; let application of unit field along the *c* direction induce in O a dipole $b_1 \times 10^{-23}$ in the *c* direction; the effect of this dipole on its neighbours in the 8-celled lattice will, by mutual induction, be the effect of the b_1's of the surrounding naphthalene molecules on O. If $+\Sigma d\bar{\mu}$ be the total moments induced in its neighbours by O, then



$$b_1 = \frac{2{\cdot}090 \times 10^{-23}}{(1 - \Sigma d\bar{\mu})} \cdot {}_RP/{}_DP$$

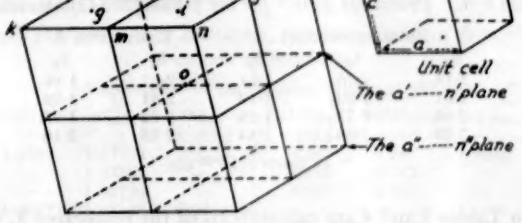
An 8-celled lattice element adequately includes induced moments of significance to O. We realise that properly the mutual effects of the atoms should be considered, as in the manner of Silberstein (*Phil. Mag.*, 1917, **33**, 92, 215, 521), but the calculation of the mutual atomic inductions of sixteen 18-atomed molecules seems to be an almost insurmountable task. We therefore regard each naphthalene molecule as "an atom group" (cf. Silberstein, *loc. cit.*) with its dipole situated at the mid-point *P* (see annexed formula) and it is the effect of this point dipole on its neighbours in the lattice (Figure) along the *c* direction that constituted the datum of Table 1. The expression used is ${}_{[4]\text{ind.}} = b_1 \times 10^{-23}(3\sin^2\alpha - 1)$ (cf. Le Fèvre, "Dipole Moments," Methuen, 3rd edn., 1953, p. 92), where *r* is the distance between the inducing and the induced dipoles, and α is (90° minus the angle between *r* and the *c* direction in the crystal). The net induction in the *c* direction at *P* in O by its neighbours in the eight cells considered is therefore $-0{\cdot}1044 \times 10^{-23}b_1$; b_1 accordingly emerges as $2{\cdot}15 \times 10^{-23}$ c.c.

The b_1, b_2, *and* b_3 *of Naphthalene.*—By means of equations (*a*) and (*b*) we can now analyse the ${}_\infty({}_mK_2)$ of naphthalene; this, in carbon tetrachloride, is found to be $48{\cdot}1 \times 10^{-12}$. Inserting $b_1 = 2{\cdot}15 \times 10^{-23}$, in conjunction with ${}_DP = 45{\cdot}4$ c.c. and ${}_RP = 41{\cdot}8$ c.c. (Le Fèvre and Rao, *Austral. J. Chem.*, 1955, **8**, 39) we derive the following tensor components: $b_1 = 2{\cdot}15 \times 10^{-23}$, $b_2 = 1{\cdot}76 \times 10^{-23}$, and $b_3 = 1{\cdot}03 \times 10^{-23}$.

TABLE 1. *Calculation of net induction at P in* O.

r = Distances		O–P (in Å)	Angle between r and c direction in crystal	$\mu_{ind.}$ at nuclear centre by O
O*a*	O*h*	15·805	33° 38′	$+0{\cdot}00273b_1$
O*b*	O*g*	11·765	21° 51′	$+0{\cdot}00972b_1$
O*c*	O*m*	10·160	31° 21′	$+0{\cdot}01133b_1$
O*d*	O*i*	7·788	34° 12′	$-0{\cdot}02227b_1$
O*e*	O*n*	9·711	64° 22′	$-0{\cdot}00479b_1$
O*f*		14·894	27° 56′	$+0{\cdot}00406b_1$
O*h*		8·680	0°	$+0{\cdot}03058b_1$
O*j*		8·143	58° 58′	$-0{\cdot}00373b_1$
Values in the $a'' \ldots j''$ plane are the counterpart of those in the $a \ldots j$ plane, therefore $\Sigma\mu_{ind.}$ in $a \ldots j$ plane $= \Sigma\mu_{ind.}$ in $a'' \ldots j''$ plane.				
O*a*′	O*e*′	$9{\cdot}833_5$	90°	$-0{\cdot}01052b_1$
O*k*′	O*n*′			
O*b*′	O*d*′	6·953	90°	$-0{\cdot}02975b_1$
O*g*′	O*i*′			
O*c*′	O*m*′	5·29	90°	$-0{\cdot}06755b_1$
O*f*′	O*j*′	8·29	90°	$-0{\cdot}01755b_1$

It is relevant to mention that ${}_\infty({}_mK_2)_{\text{naphthalene}}$ has hitherto been recorded in carbon tetrachloride only once: Otterbein (*Physikal. Z.*, 1934, **35**, 264) quoted it as 42×10^{-12} but presented no supporting details of his actual measurements. Grodde's value for molten naphthalene at 80° ($33{\cdot}9 \times 10^{-12}$; *ibid.*, 1938, **39**, 772) corresponds to $40{\cdot}2 \times 10^{-12}$ at 25°.



Briegleb (*Z. physikal. Chem.*, 1936, **16**, *B*, 249), using heptane as solvent, deduced ${}_mK_2$ as 110×10^{-12}—a figure of the order to be expected from available data for the Δ of naphthalene vapour (cf. Cabannes, "La Diffusion Moléculaire de la Lumière," Les Presses Universitaires de France, 1929, p. 254). We have previously commented (*J.*, 1954, 1577) on the uncertainty attending extant depolarisation factors. Briegleb does not show the B_1, n_1, ϵ_1, or d_1 for his heptane; when these are taken respectively as 0·071 × 10^{-7}, 1·388, 1·924, and 0·684 (*i.e.*, for 20°), and his observations extrapolated by our method (*J.*, 1953, 4041), an ${}_\infty({}_mK_2)$ of about 40×10^{-12} is derived. (As both Grodde and Briegleb computed their ${}_mK$'s by a formula lacking a 6 used by us, their measurements have been multiplied accordingly for quotation in the preceding text.)

Halogenonaphthalenes.—The molar Kerr constants, at infinite dilution in carbon tetrachloride at 20° for light of $\lambda = 5893$ Å, of the eight monohalogenonaphthalenes are listed in Table 2. Otterbein (*loc. cit.*) cites ${}_mK$ values for two of these substances in carbon tetrachloride: α-$C_{10}H_7Cl$, 165×10^{-12}; β-$C_{10}H_7Cl$, 427×10^{-12}; his results resemble ours in order, but since he gives no experimental data we cannot decide whether the differences

TABLE 2. *Molar Kerr constants at infinite dilution.*

Solute	${}_\infty({}_mK_2) \times 10^{12}$	Solute	${}_\infty({}_mK_2) \times 10^{12}$
α-$C_{10}H_7F$	72·6	α-$C_{10}H_7Br$	213
β-$C_{10}H_7F$	233	β-$C_{10}H_7Br$	469
α-$C_{10}H_7Cl$	190	α-$C_{10}H_7I$	244
β-$C_{10}H_7Cl$	406	β-$C_{10}H_7I$	490

lie in the observations or merely in the extrapolation procedure used. Otterbein thought the constant for β-chloronaphthalene to be extraordinarily high; it is now clear that generally throughout the four pairs of isomeric halogenonaphthalenes $({}_mK_2)_{\beta\text{-isomer}}$ is notably greater (2—3 times) than $({}_mK_2)_{\alpha\text{-isomer}}$.

Polarisability Ellipsoids of Halogenonaphthalenes.—No depolarisation factors for halogenonaphthalenes in the vapour state exist. Lacking equation (*c*), therefore, we have compounded b_3 in each case as follows:

$$b_3^{C_{10}H_7X} = b_3^{C_{10}H_8} - b_L^{(C-H)_{aryl}} + b_L^{(C-X)_{aryl}}$$

and used it in conjunction with our ${}_\infty({}_mK_2)$ and the average polarisability, the values $b_L^{(C-X)_{aryl}}$ being those quoted in *J.*, 1954, 1577. Further, in view of the absence of polarisation–temperature data for these compounds as gases, we have assumed, in equation (*b*), that ${}_DP/{}_EP = 1{\cdot}1$, and in equation (*a*) that ${}_EP = 0{\cdot}95R_D$. We have taken b_3 to be the same for each pair of isomers, and have located b_1 along (or parallel to) the direction of action of $\mu_{C_{10}H_7X}$. Results are shown in the first parts of Tables 3 and 4.

TABLE 3. *Principal axes * for the α-halogenonaphthalenes.*

	From experiment			Calculation A		Calculation B	
	b_1	b_2	b_3	b_1	b_2	b_1	b_2
α-$C_{10}H_7F$	1·71	2·19	1·01	1·78	2·15	1·74	2·13
α-$C_{10}H_7Cl$	2·31$_5$	2·09	1·19	2·12	2·28	2·06	2·43
α-$C_{10}H_7Br$	2·39	2·14$_5$	1·28	2·33	2·25	2·17	2·40
α-$C_{10}H_7I$	2·77	2·13	1·44	2·63	2·45	2·38	2·56

TABLE 4. *Principal axes * for the β-halogenonaphthalenes.*

	From experiment			Calculation A		Calculation B	
	b_1	b_2	b_3	b_1	b_2	b_1	b_2
β-$C_{10}H_7F$	2·14	1·76	1·01	2·07	1·86	2·12	1·84
β-$C_{10}H_7Cl$	2·61	1·79$_5$	1·19	2·41	1·99	2·31	2·02
β-$C_{10}H_7Br$	2·85	1·71	1·28	2·62	1·96	2·46	2·11
β-$C_{10}H_7I$	3·23	1·83	1·44	2·92	2·16	2·67	2·27

* In units: 10^{-23} c.c.

Also included in Tables 3 and 4 are calculations of the respective b_1's and b_2's, made by the additivity equations (*d*) and (*e*) for the α-, and (*f*) and (*g*) for the β-, isomers:

$$b_1^{C_{10}H_7X} = b_2^{C_{10}H_8} - b_L^{C-H} + b_L^{C-X} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (d)$$

$$b_2^{C_{10}H_7X} = b_1^{C_{10}H_8} - b_V^{C-H} + b_V^{C-X} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (e)$$

$$b_1^{C_{10}H_7X} = b_1^{C_{10}H_8} \cdot \cos^2 30° + b_2^{C_{10}H_8} \cdot \sin^2 30° - b_L^{C-H} + b_L^{C-X} \quad . \quad . \quad (f)$$

$$b_2^{C_{10}H_7X} = b_1^{C_{10}H_8} \cdot \sin^2 30° + b_2^{C_{10}H_8} \cdot \cos^2 30° - b_V^{C-H} + b_V^{C-X} \quad . \quad . \quad (g)$$

The b_L's and b_V's are those listed in *J.*, 1954, 1577; the calculations denoted by A and B differ in that A utilises bond polarisabilities previously deduced from aromatic structures whilst B uses those derived from aliphatic molecules.

By subtracting the *b*'s from "calculation B" from those "from experiment" we obtain estimates of exaltations (Δb_1 and Δb_2). These are listed as Table 5. Except where fluorine is concerned, positive exaltations are seen in the C–Halogen bond directions—the situation is thus qualitatively analogous to that reported for the halogenobenzenes (*J.*, 1954, 1577 †). Table 5 suggests that the *average* polarisabilities for these molecules should not show marked exaltations; that this is so may be seen from Table 6, referring to R_D values; the column under $(R_D)_{calc.}$ is composed from the following: $R_{naphthalene} = 44{\cdot}37$ c.c., $R_{C-H} = 1{\cdot}68$, $R_{C-F} = 1{\cdot}44$, $R_{C-Cl} = 6{\cdot}51$, $R_{C-Br} = 9{\cdot}39$, and $R_{C-I} = 14{\cdot}61$ (Vogel, Cresswell, Jeffery, and Leicester, *J.*, 1952, 530).

† "Table 4," 4 lines from the bottom of p. 1582 of this reference, should read "Table 5."

TABLE 5. *Exaltations in the* b_1 *and* b_2 *directions.*

	Δb_1	Δb_2		Δb_1	Δb_2
α-$C_{10}H_7F$	−0·03	+0·06	β-$C_{10}H_7F$	+0·02	−0·08
α-$C_{10}H_7Cl$	+0·25$_5$	−0·34	β-$C_{10}H_7Cl$	+0·30	−0·22$_5$
α-$C_{10}H_7Br$	+0·22	−0·25$_5$	β-$C_{10}H_7Br$	+0·39	−0·40
α-$C_{10}H_7I$	+0·39	−0·43	β-$C_{10}H_7I$	+0·56	−0·44

TABLE 6. *Calculated and observed molecular refractions (in c.c.) (D-line).*

	$(R_D)_{calc.}$	$(R)_{obs.}$ for α-isomers	$(R)_{obs.}$ for β-isomers
$C_{10}H_7F$	44·13	43·7	43·7
$C_{10}H_7Cl$	49·20	49·2	49·4
$C_{10}H_7Br$	52·08	51·6	51·8
$C_{10}H_7I$	57·30	56·5	57·9

EXPERIMENTAL

Materials.—The naphthalene and halogenated naphthalenes were spectroscopically pure specimens kindly lent by Mr. A. Ferguson, to whom we express our gratitude. The carbon tetrachloride (sulphur-free) was a gift of a " middle cut " of the fractionation plant of Imperial Chemical Industries (Australia and New Zealand Ltd.) whom we also thank.

Measurements.—These were made by our method previously described (*J.*, **1953**, **4041**), where the symbols used here are defined and the extrapolation procedure is explained. The observations recorded in Table 6 are for either 20° or 25°, at which temperatures the following data for the solvents are taken.

Temp.	10^7B_D	n_D^1	d_4^1	ε_1	H	J	$10^{14}{}_sK_1$
20°	0·072	1·4604	1·5940	2·2360	2·064	0·4721	0·761
25°	0·070	1·4575	1·5845	2·2270	2·060	0·4731	0·749

TABLE 7. *Weight fractions, Kerr constants, refractive indexes, densities, and dielectric constants of solutions.*

Naphthalene in carbon tetrachloride at 25°

10^5w_2	10^7B_{12}	$(n_D^1)_{12}$	$(d_4^1)_{12}$	$(\varepsilon_1)_{12}$	10^5w_2	10^7B_{12}	$(n_D^1)_{12}$	$(d_4^1)_{12}$	$(\varepsilon_1)_{12}$
309	0·085	—	—	2·2288	3514	0·179	—	—	—
840	0·101	1·4597	1·57774	2·2322	4265	0·267	1·4689	1·55005	2·2545
1319	0·116	—	1·57363	—	4389	0·213	—	1·54759	—
2098	0·139	—	1·56728	—	4537	0·220	—	—	—
2356	0·150	1·4637	1·56528	2·2416					

whence $\Delta B = 3{\cdot}43_2w_2 - 4{\cdot}5w_2^2$

α-Fluoronaphthalene in carbon tetrachloride at 20°

152	0·082	—	1·5928$_5$	2·2404	1278	0·133	1·4629	1·5863	2·2730
166	0·083	—	1·5927	2·2410	1641	0·153	1·4635	1·5835	2·2836
561	0·102	1·4614	1·5903	2·2503	2300	0·184	1·4650	1·5795	2·3042

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 4{\cdot}81$

β-Fluoronaphthalene in carbon tetrachloride at 20°

334	0·121	1·4610	1·5922	2·2464	855	0·199	1·4621	1·5889	2·2647
374	0·131	1·4611	1·5918	2·2486	1413	0·283	1·4632	1·5853	2·2846
747	0·182	1·4619	1·5895	2·2607					

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 14{\cdot}91$

α-Chloronaphthalene in carbon tetrachloride at 20°

871	0·163	1·4625	1·5897	2·2624	2265	0·317	—	—	—
1532	0·240	—	1·5867	2·2868	2765	0·375	1·4675	1·5805	2·3238
1634$_5$	0·248	1·4640	—	—	4040	0·517	—	—	—
1640	0·250	—	1·5863	2·2876					

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 10{\cdot}93$

β-Chloronaphthalene in carbon tetrachloride at 20°

322	0·148	—	—	—	1088	0·322	1·4662	1·5884	2·2787
634	0·221	1·4651	1·5908	2·2605	1245	0·361	—	—	—
680	0·232	—	—	—	1408	0·406	1·4671	1·5867	2·2906

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 23{\cdot}39$

TABLE 7. *Continued.*

α-Bromonaphthalene in carbon tetrachloride at 20°

10^5w_2	10^7B_{12}	$(n_D^2)_{12}$	$(d_4^4)_{12}$	$(\varepsilon_1)_{12}$	10^5w_2	10^7B_{12}	$(n_D^2)_{12}$	$(d_4^4)_{12}$	$(\varepsilon_1)_{12}$
737	0·150	1·4621	1·5933	2·2530	1706	0·240	—	—	—
981	0·168	1·4625	1·5930	2·2612	2255	0·280	1·4652	1·5921	2·2947
1522	0·221	—	—	—	2589_5	0·326	—	—	—

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 9{\cdot}43$

β-Bromonaphthalene in carbon tetrachloride at 20°

311	0·139	1·4610	1·5935	2·2450	1210	0·330	1·4629	1·5924	2·2711
445	0·169	—	—	—	1474	0·387	—	—	—
905	0·262	—	—	—	1525	0·394	$1·4638_5$	1·5920	2·2795

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 21{\cdot}25$

α-Iodonaphthalene in carbon tetrachloride at 20°

536	0·128	1·4615	1·5948	2·2452	2007	0·253	—	—	—
1161	0·184	1·4629	1·5959	2·2599	2338	0·274	—	1·5979	2·2840
1382	0·197	—	—	—	6067	—	1·4746	1·6037	2·3579
1595	0·228	1·4641	1·5965	2·2679					

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 9{\cdot}53$

β-Iodonaphthalene in carbon tetrachloride at 20°

276	0·122	1·4609	1·5943	2·2417	706	0·197	1·4620	1·5950	2·2509
335	0·133	—	—	—	905	0·238	1·4625	1·5954	2·2567
462	0·150	—	1·5946	2·2455	983	0·253	1·4629	1·5955	2·2585

whence $\Sigma(\Delta B \,.\, w_2)/\Sigma w_2^2 = 18{\cdot}12$

TABLE 8. *Calculation of molar Kerr constants and dipole moments at infinite dilution in carbon tetrachloride.*

Temp.	Solute	$\alpha\varepsilon_1$	β	γ	δ	$_\infty(_mK_2) \times 10^{12}$	$_\infty P_2$	(R_D)	μ, D
25°	Naphthalene	0·617	−0·515	0·181	49·0	48·1	44·0	—	0
20	α-Fluoronaphthalene	3·03	−0·400	0·133	$66·8_5$	72·6	83·9	43·7 [1]	1·39
20	β- ,, ,,	3·36	−0·376	0·134	207·1	233·1	$88·3_5$	,,	1·47
20	α-Chloronaphthalene	3·18	−0·302	0·166	151·8	189·8	93·0	49·2 [2]	1·45
20	β- ,, ,,	3·89	−0·323	0·166	324·9	406·2	105·7	49·4 [2]	1·65
20	α-Bromonaphthalene	2·54	−0·057	0·148	131·0	213·4	95·2	51·6 [2]	1·45
20	β- ,, ,,	2·88	−0·085	0·147	295·1	468·6	103·7	51·8 [2]	1·58
20	α-Iodonaphthalene	2·01	0·101	0·160	125·5	244·2	95·4	56·5 [3]	1·37
20	β- ,, ,,	2·20	0·090	0·151	251·4	489·9	101·0	57·9 [3]	1·44

[1] Parts (*Z. physikal. Chem.*, 1930, *B*, **10**, 264). [2] Auwers and Frühling (*Annalen*, 1921, **422**, 192).
[3] Krollpfeiffer (*Annalen*, 1923, **430**, 161).

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Interconversions of Itaconic and Citraconic Anhydride in Amine Solutions.

By W. G. Barb.

[Reprint Order No. 51013.]

The isomerization of itaconic to citraconic anhydride in dimethylaniline solution has been shown spectrophotometrically to be a first-order reaction; the activation energy is about 15 kcal./mole and the temperature-independent factor about $2{\cdot}5 \times 10^9$ min.$^{-1}$. Other complex-forming aromatic solvents, *e.g.*, anisole or mesitylene, do not catalyse the conversion to a significant extent.

Aliphatic tertiary amines and itaconic anhydride instantaneously form a deep-magenta-coloured complex which then slowly changes to an unidentified reddish-brown product; the same product is also formed slowly from citraconic anhydride in aliphatic amine solution. Ammonia and primary and secondary amines also instantaneously form magenta complexes with itaconic anhydride, but these fade extremely rapidly owing to amide formation. A solution of itaconic anhydride is suggested as an easy specific reagent for tertiary aliphatic amines.

During investigations on coloured molecular complexes of maleic anhydride and its derivatives Pfeiffer and Böttler (*Ber.*, 1918, **51**, 1819) observed that dimethylaniline catalysed the isomerization of itaconic anhydride to citraconic anhydride. Citraconic anhydride dissolved in dimethylaniline instantaneously gives an orange colour, ascribable to a molecular complex. Itaconic anhydride gives a solution which is initially pale yellow but slowly assumes the same colour as the citraconic anhydride solution; when such a solution is treated with alkali and then acidified, citraconic acid is obtained. In the absence of a solvent the conversion of itaconic into citraconic anhydride only takes place at high temperatures (cf. *Org. Synth.*, Coll. Vol. II, John Wiley & Sons, Inc., New York, 1943; also p. 1650).

Two causes of the catalytic effect of dimethylaniline suggest themselves: the reaction may simply be base-catalysed; or the ease of isomerization in dimethylaniline may be linked in some way with the formation of a complex between the solvent and the product. At its simplest, the latter may be regarded as a lowering of the energy level of the transition state accompanying the lowering of the energy level of the final state. (A simple inorganic example is the increased rate of autoxidation of ferrous ions in the presence of substances which form complexes with ferric ion.) Since, according to Pfeiffer and Böttler (*loc. cit.*), durene, methyl *o*-tolyl ether, and quinol (all of which form complexes with citraconic anhydride) do not cause the isomerization of itaconic anhydride, it seemed *a priori* more probable that the isomerization in dimethylaniline is due to the basic nature of the solvent.

Spectrophotometric Measurements in Dimethylaniline Solution

Materials.—Dimethylaniline was freed from primary and secondary amines by refluxing with acetic anhydride, and was then fractionally distilled through a 12″ column containing Fenske helices. Citraconic anhydride was a commercial sample, fractionally redistilled under reduced pressure (b. p. 71°/7 mm.). Itaconic anhydride was prepared from commercial itaconic acid and thionyl chloride (Meyer, *Monatsh.*, 1901, **22**, 422) and was twice recrystallized (m. p. 65—66°) from chloroform–ether.

Technique of Measurement.—Optical density was measured (*a*) on a Unicam Quartz Spectrophotometer Model S.P. 500, using 1 cm. or 2 mm. cells, and (*b*) on a Hilger " Spekker " absorptiometer, using a mercury lamp source, Ilford Filter 603 to isolate the 4916 Å line or a combination of Ilford Filter 605 and Chance Filter OB2 to isolate the 5461 Å line, and 2·5 mm. or 5 mm. cells. Experiments with the Unicam instrument were carried out at room temperature but measurements on the Spekker absorptiometer were made with the cells carried in a small thermostat bath mounted on the slide. The cell containing the blank and an empty cell were kept in the thermostat for some minutes, the solution of itaconic anhydride then made up as rapidly as

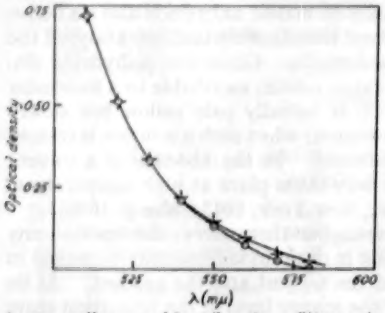
possible (finely powdered, it dissolves in dimethylaniline in a matter of seconds), and poured into the cell, this point being taken as zero time.

All measurements were carried out against blanks of dimethylaniline. Calibration curves were constructed; with the Unicam instrument, the D–[citraconic anhydride] plot is linear, where D is the optical density. With the Spekker arrangement, the plots were slightly curved, to an extent indicating about 98% monochromatization. The optical density of itaconic anhydride solutions, extrapolated to zero time, was always negligible (less than 0·01).

The optical density of citraconic anhydride solutions in dimethylaniline decreases by about 7% from 20° to 50°, and this was taken into account in using the calibration curves. No deduction regarding the heat of formation of the absorbing citraconic anhydride–dimethylaniline complex can be made from this, since it is not known whether the equilibrium constant is large or small; if large, it is clear that little change of optical density with temperature would be expected in any case since the fraction of citraconic anhydride present as a complex would remain near unity.

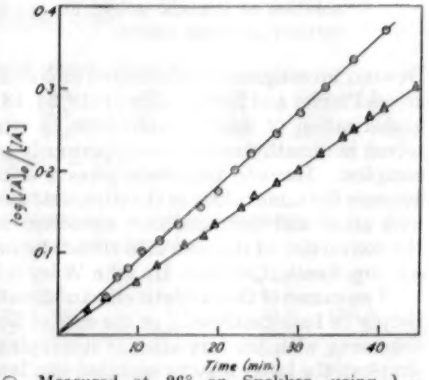
Quantitative Nature of the Conversion, and Kinetic Results.—It is relatively easy to obtain experimental conditions where the optical density of an itaconic anhydride solution after

FIG. 1. *Optical density of citraconic and itaconic anhydride solutions in dimethylaniline.*



1 cm. cells; c, 10 g./l. ○ = Citraconic anhydride; + = itaconic anhydride after overnight standing.

FIG. 2. *Typical first-order plots.*



○, Measured at 26° on Spekker, using λ = 5641 Å. △, measured at 22° on Unicam, using λ = 5400 Å. Both solutions contained 0·5 g./l. of quinol. $[IA]_0$ = 30 g./l.

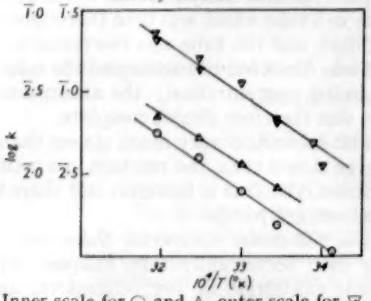
prolonged storage (say overnight) is within ±10% of that for a citraconic anhydride solution. An improvement is difficult as there are two vitiating factors: In dilute solutions of the anhydrides (say <0·5%) traces of water can produce appreciable fading due to hydrolysis. In more concentrated solutions the fading is negligible, but itaconic anhydride induces the autoxidation of dimethylaniline to produce an impurity which absorbs in the yellow region of the spectrum; in such solutions the optical density of citraconic anhydride and "old" itaconic anhydride solutions agree perfectly at shorter wavelengths, but at long wavelengths, the old itaconic anhydride solution has a greater density (cf. Fig. 1). This autoxidation could be roughly halved by the addition of small quantities of quinol to the dimethylaniline. Such solutions gave final optical densities in reasonable agreement with the expected value (within about 5%) even at long wavelengths, if measured against a solution of quinol and dimethylaniline of the same age. Most of the kinetic measurements were carried out in this way (Table). Since the available wavelengths (5461 and 4916 Å) and cells largely determined the concentration of itaconic anhydride which could be used in the kinetic experiments, it was impossible to avoid both the fading and the autoxidation difficulties simultaneously. For λ 5461 Å, fairly concentrated solutions had to be used (of the order 30 g./l.) and the final optical density was (in the absence of quinol) up to 15% higher than the value to be expected if only citraconic anhydride had been produced; for λ 4916 Å, on

First-order velocity constant k for conversion of itaconic anhydride in dimethylaniline solution.

Temp.	Instrument	λ (Å)	$[IA]_0$ (g./l.)	[Quinol] (g./l.)	10^5k (min.$^{-1}$)	Temp.	Instrument	λ (Å)	$[IA]_0$ (g./l.)	[Quinol] (g./l.)	10^5k (min.$^{-1}$)
21° ± 1°	Unicam	5300	25·0	—	1·24	26°	Spekker	5461	30·5	—	2·67
,,	,,	5300	5·0	—	1·13	30	,,	,,	30·3	—	3·68
,,	,,	5400	30·3	0·5	1·22	35	,,	,,	29·7	—	5·28
,,	,,	5400	30·3	1·0	1·25	40	,,	,,	30·0	—	7·15
22 ± 1	,,	5400	30·4	0·5	1·56						
						26	,,	,,	29·9	0·5	2·07
26	Spekker	4916	5·0	—	1·56	,,	,,	,,	30·5	,,	2·13
30	,,	,,	5·0	—	2·53	30	,,	,,	29·6	,,	3·63
35	,,	,,	5·5	—	4·02	35	,,	,,	29·9	,,	4·30
40	,,	,,	5·1	—	5·68	,,	,,	,,	30·2	,,	5·12
						40	,,	,,	29·8	,,	6·43
						,,	,,	,,	30·9	,,	7·12

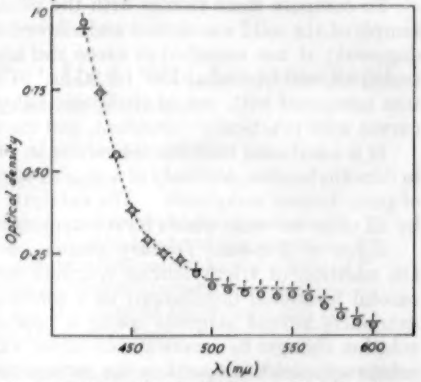
the other hand, the density was up to 15% too low. These errors are of course most significant near the end of the reaction, since the concentration of itaconic anhydride [IA] is calculated as the difference between the initial concentration $[IA]_0$ and the (apparent) amount

FIG. 3. *Temperature-dependence of first-order velocity constant k.*



Inner scale for ○ and △, outer scale for ▽.
○ measured at λ = 4916 Å, $[IA]_0$ ~5 g./l.
△ measured at λ = 5461 Å, $[IA]_0$ ~30 g./l.
▽, as △, but 0·5 g./l. of quinol added.

FIG. 4. *Optical density of itaconic (+) and citraconic (○) anhydride in acetone containing 0·5% of triethylamine, after standing at room temperature for 48 hr.*



Concentration of anhydrides = 5·0 g./l.; 1 cm. cells.

of citraconic anhydride formed. Consequently, kinetic runs were usually only evaluated to about 60% conversion; some typical results are shown in Fig. 2, which demonstrates that log $[IA]_0/[IA]$ is linear with time, *i.e.*, that the reaction is of first order in [IA]. This first order is also demonstrated by the agreement between values of *k* obtained from experiments at widely different values of $[IA]_0$ (cf. Table).

The various values of *k* obtained are given in the Table. It is seen that the measured values for λ 5461 and 4916 Å differ by about 30%, in the sense to be expected from the sources of error just discussed.

The effect of temperature on *k* is shown in Fig. 3. Though the values of *k* fall into three groups, for the reasons discussed, the values of the activation energy agree well, being 14·5, 15·4, and 15·6 kcal./mole respectively; from a mean value of 15·2 kcal./mole, the temperature-independent factor is found to be $2·5 \times 10^9$ min.$^{-1}$.

Attempts were made to examine the effect of dimethylaniline concentration on the reaction rate, using various diluents. These all failed; the autoxidation of dimethylaniline in the presence of itaconic anhydride was much more pronounced when diluents were used, and could not be adequately suppressed.

Effect of Other Complex-forming Aromatic Solvents.—The stability of itaconic anhydride in benzene, mesitylene, and anisole, which are known to form complexes with maleic anhydride

and therefore presumably also with citraconic anhydride (Barb, *Trans. Faraday Soc.*, 1953, **49**, 143), was examined. In all cases the ultraviolet absorption of citraconic anhydride solutions is much more pronounced than that of itaconic anhydride solutions, so that any conversion was easily detectable.

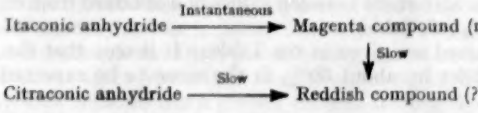
Solutions of itaconic anhydride in benzene were refluxed for up to 11 days; the increase in optical density, if attributed to formation of citraconic anhydride, corresponded to less than 4% conversion. Solutions of itaconic anhydride in mesitylene showed no evidence of isomerization after 24 hr. at 60°. At higher temperatures (130° and 160°) experiments had to be carried out in sealed tubes *in vacuo*, to prevent oxidative side-reactions leading to strongly absorbing products. Under these conditions the isomerization undoubtedly occurs in mesitylene but is still quite slow, *e.g.*, at 160° about 10% was converted in 5 hr. and about 70% in 100 hr. Solutions in anisole behaved similarly, *e.g.*, during 24 hr. about 20% was converted at 130° and about 60% at 160°. In each case it was found that a small quantity of by-product was formed, since the solutions of itaconic anhydride which had been heated showed a slight but definite absorption at wavelengths longer than those at which solutions of citraconic anhydride absorb; at shorter wavelengths the shape of the optical density–wavelength curve was identical with that for citraconic anhydride solution, showing that this was the main product. It was observed that the yield obtained tended to be unduly low in very dilute solutions; this was attributed to hydrolysis by traces of water.

To compare these results with the behaviour of pure itaconic anhydride on heating, a sample of the solid was melted and allowed to resolidify in a tube which was then thoroughly degassed; it was remelted *in vacuo* and again resolidified, and the tube was re-evacuated, sealed off, and heated at 130° for 20 hr. The product was dissolved in anisole and the solution compared with one of citraconic anhydride of similar concentration; the absorption curves were practically coincident, and the conversion was therefore almost complete.

It is concluded that the conversion in other aromatic solvents is very much slower than in dimethylaniline, and only of a similar speed to, or even slower than, the reaction in a melt of pure itaconic anhydride. The catalytic effect of dimethylaniline is therefore not shared by all other solvents which form complexes with citraconic anhydride.

Effect of Aliphatic Tertiary Amines on Itaconic and Citraconic Anhydride Solutions.—On addition of triethylamine (purified by refluxing with acetic anhydride, followed by careful fractional distillation) to a solution of itaconic anhydride in, say, chloroform an extremely intense magenta colour is produced. In a few hours at room temperature the solution changes to a more stable colour varying from purple to reddish-brown. (The final colour appears to depend on the concentrations used and on the diluent; thus solutions in acetone give a more orange colour than those in chloroform.)

In contrast, citraconic anhydride solutions on addition of triethylamine initially give only a pale yellow colour, but in a few hours this intensifies to the reddish colour obtained from the itaconic anhydride solutions. The identical absorption of the final solutions, after 48 hours, is shown in Fig. 4. The reactions with triethylamine are thus:



The magenta-coloured compound is regarded as a loose molecular complex in view of its instantaneous formation when the reagents are mixed, even at low temperatures. Thus, *e.g.*, a 1% solution of itaconic anhydride in chloroform was degassed *in vacuo* and kept frozen in liquid air, and a quarter of its volume of triethylamine was distilled in; when this mixture was allowed to thaw in carbon dioxide–acetone at −60° the magenta colour was formed immediately. At −60° the complex appeared completely stable; at 0° the magenta colour became more brown during several hours.

The nature of the final, stable compound obtainable from the anhydrides was not established. Reaction with pure liquid citraconic anhydride and triethylamine is violent and gives a brittle purplish-black solid which dissolves not only in chloroform but also in

water to give a clear intensely coloured solution. In water, this colour fades completely after a few hours.

A variety of compounds structurally related to the anhydrides (itaconic acid, butyl acrylate, maleic anhydride, benzoquinone) were added to triethylamine in chloroform. In each case only a slight yellow colour or no effect at all was produced. As regards different bases, tertiary aliphatic amines as diverse as triethylamine, *N*-ethylethyleneimine, and 1 : 4-di-*n*-butylpiperazine all give similar intense colours with itaconic anhydride. Primary and secondary amines, and even ammonia, give momentary magenta reactions, but the colours in these cases fade extremely rapidly, presumably owing to amide formation. It appears therefore that the formation of the magenta-coloured complexes is highly specific to itaconic anhydride, but shared by all aliphatic amines. The subsequent formation of a more stable coloured compound is only shown by tertiary amines because amide formation cannot supervene. A solution of itaconic anhydride in chloroform is suggested as a sensitive specific reagent, easy to use, for detection of tertiary aliphatic amines.

It is concluded that the catalysis by dimethylaniline of the isomerization of itaconic to citraconic anhydride is a highly specific effect. It is not shown by other aromatic solvents or by aliphatic tertiary amines.

COURTAULDS LTD., RESEARCH LABORATORY,
LOWER COOKHAM ROAD, MAIDENHEAD, BERKS. [*Received, December 29th*, 1954.]

Absorption Spectra of Ketones. Part III. The Long-wavelength Band of αβ-Unsaturated Ketones.*

By R. C. COOKSON and S. H. DANDEGAONKER.

[Reprint Order No. 6016.]

The absorption spectra of some αβ-unsaturated ketones have been measured in *n*-hexane solution from 280 to 400 mμ. The wavelength of the maximum of the weak band occurring in this region is mainly determined by the degree of alkylation of the double bond, substitution shifting it to shorter wavelengths. No simple relation was found between the structure of the ketone and the degree of vibrational fine structure of the absorption band.

ALKYL substitution on the α- and the β-carbon atom of an αβ-unsaturated aldehyde or ketone causes a predictable shift in the wavelength of the maximum of intense ultraviolet absorption (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Evans and Gillam, *J.*, 1941, 815; 1943, 565; Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 3rd Edn., p. 190) but little is known about the effect of structure on the position or intensity of the weak band that occurs at longer wavelengths in these spectra. The absorption of a variety of αβ-unsaturated ketones, mostly *cyclo*hexenones, has therefore been measured in the region 280—400 mμ.

The weak band has been characterised as due to an $n \rightarrow \pi$ transition, both by calculation of the expected intensity of the transition (McMurray, *J. Chem. Phys.*, 1941, **9**, 231) and by consideration of the solvent effect (McConnell, *ibid.*, 1952, **20**, 700). Since change of solvent from hydrocarbon to ethanol shifts the intense band to longer but the weak one to shorter wavelengths, the latter often appears, in ethanol, only as an inflection superimposed on the end-absorption of the main band. Although most published information on the absorption spectra of αβ-unsaturated ketones refers to ethanol solutions and records the intense band only, there are ample data to show that the maximum of the weak band of most open-chain αβ-unsaturated ketones, *cyclo*hexenones and 2-alkylidene*cyclo*hexanones in ethanol occurs between about 300 and 330 mμ. *cyclo*Pentenones seem to absorb near the lower end of this range, whereas 2-alkylidene*cyclo*pentanones form a class characterised by the exceptionally long wavelength and rather greater intensity of the weak band (Table 1). The

* Part II, *J.*, 1955, 352.

TABLE 1. *Derivatives of 2-methylenecyclopentanone in ethanol.*

No.	Substance	$\lambda_{max.}$	ε	Ref.
1	4-Methyl-2-*iso*propylidene*cyclo*pentanone	340 [a,b]	60	1
2	3β-Acetoxy-16-*iso*propylideneandrost-5-en-17-one	338	100	2
3	16-*iso*Propylideneandrosta-3 : 5-dien-17-one	338 [b]	60	2
4	3β-Acetoxycholest-8(14)-en-15-one	339	109	3
5	Anhydro-oxoelemadienyl acetate-I	342—345	86	4
6	3β-Hydroxy-22*a* : 5α-C-nor : D-homospirost-13(17*a*)-en-11-one	350	76 [a]	5
7	Diacetyljervine	360	80	6
8	3β : 17 : 23-Trihydroxy-22 : 26-iminojerva-5 : 13(17*a*)-dien-11-one 3 : 23 : *N*-triacetate	355	85	7

[a] Dr. R. F. Hirschmann has kindly informed us that log ε 2·88 quoted for this band (*J. Amer. Chem. Soc.*, 1954, **76**, 4013) should read log ε 1·88.
[a] Inflection. [b] Approx. wavelength read from small-scale graph.

position of the band in the anhydro-ketone derived from acetoxyelemadienic acid (No. 5) can therefore be taken as indicating the 2-*iso*propylidene*cyclo*pentanone chromophore, a conclusion already reached from other spectroscopic evidence (Halsall, Meakins, and Swayne, *J.*, 1953, 4139). (Substitution by hetero-atoms in certain conformations α′ or γ to the carbonyl group of the other classes of αβ-unsaturated ketones may shift the weak band into the same region : examples will be discussed in a later paper.)

In order to secure greater separation of the two absorption bands and thus better resolution of the weak one, and also to investigate the vibrational fine structure of the latter, our measurements have been made in *n*-hexane. Amongst saturated ketones, open-chain ketones and most *cyclo*hexanones show no fine structure even in paraffinic solvents, but *cyclo*pentanone (Benson and Kistiakowsky, *J. Amer. Chem. Soc.*, 1942, **64**, 80; Biquard, *Bull. Soc. chim. France*, 1941, **8**, 55, 725) and *cyclo*butanone (Benson and Kistiakowsky, *loc. cit.*) do show fine structure in *n*-hexane. Few accurate measurements are available of the $n \rightarrow \pi$ band of αβ-unsaturated ketones; those that are have been included in the Tables. (Unless otherwise indicated, the following discussion refers only to this band in *n*-hexane.)

In drawing up the Tables we have followed Mohler (*Helv. Chim. Acta*, 1937, **20**, 289) in designating successive bands by Roman letters, starting with the band of longest wavelength. Although either C or D may be the most intense band (ε shown in parentheses) the general shapes of the various absorption curves showing resolved fine structure are so similar that corresponding bands can be picked out with confidence. Band A is usually about a third to a quarter as intense as C and D, and the difference in frequency between A and B is usually rather greater than that between other pairs of successive bands. In fact band A of the ketones seems to correspond with the two longest wavelength bands of acraldehyde (No. 9). Bands of ketones not showing a complete progression, owing to poorly developed vibrational structure, have been lettered with fair confidence by careful comparison with examples showing well-developed vibrational structure. For ketones showing little or no fine structure assignment of maxima to particular vibrational bands is unjustified. These maxima are printed in italics.

Consideration of the wavelengths of corresponding maxima in the spectra of *cyclo*hexenones (Tables 3—6) clearly shows that the most important factor in determining the position of a particular band is the degree of alkyl substitution on the double bond : Amongst the monocyclic *cyclo*hexenones and the polycyclic ones having the chromophore in a terminal ring, one α- or β-alkyl substituent causes a shift of about 6 mμ to shorter wavelengths, and two alkyl substituents cause a shift of about 20 mμ in the same direction. Whether or not the β-alkyl group is exocyclic to another six-membered ring appears immaterial (compare Nos. 18 & 19) (cf. the intense band; Woodward, *loc. cit.*, 1942), and the only effect of methylation of the α-carbon atom is to increase the extinction and reduce the resolution of the vibrational structure somewhat without effecting the wavelengths of the component bands (compare Nos. 13 & 14). Amongst the *cyclo*hexenones having the chromophore in a central ring of a polycyclic system the wavelengths of corresponding bands still seem usually to be determined by the degree of alkylation of the double bond, but there are several notable deviations (Nos. 23, 24, 26—28, 33) that presumably indicate the operation of more subtle influences, perhaps of steric origin.

TABLE 2. *αβ-Unsaturated aldehydes.*

No.	Substance	A	B	C	D	E	F	Ref.
9	Acraldehyde	385·2(6·5) 378·5(6·2)	366·5(10·7)	349·2(11·5)	334·8(11·6)	—	—	8
10	α-Methylacraldehyde	370 [a] (6)	360 [a] (16)	—	330(26)	—	—	9
11	β-Methylacraldehyde	370 [a] (7)	360 [a] (16)	—	330(25)	—	—	9

TABLE 3. *Unsubstituted* cyclo*hex-2-enones.*

No.	Substance	A	B	C	D	E	F	Ref.
12	*trans*-$\Delta^{3:6}$-Hexahydro-10-methyl-2-oxonaphthalene	373 [a] (8)	355(20)	342(26)	332(25)	322 [a] (23)	313 [a] (21)	3
13	Cholest-1-en-3-one	374(9·5)	357(21)	344(27·5)	333(26)	322·5 [a] (23)	—	3
14	β-Amyra-1 : 12-dien-3-one	—	359 [a] (48)	344(63)	332(66)	321 [a] (59)	—	3
15	Cholest-2-en-1-one	—	350(50)	342(54)	331(49)	318·5 [a] (37)	—	3

TABLE 4. 2-*Substituted* cyclo*hex-2-enones.*

No.	Substance	A	B	C	D	E	F	Ref.
16	2-Methyl*cyclo*hex-1-en-3-one	369(3·5)	351(9·5)	337(14)	327(18)	315(18)	—	3
17	Carvone	370	356	340	327	313	—	10

TABLE 5. 3-*Substituted* cyclo*hex-2-enones.*

No.	Substance	A	B	C	D	E	F	Ref.
18	*iso*Phorone	368(9)	349(22·5)	337(30)	325(29)	—	—	3
19	Cholest-4-en-3-one	367 [a] (22)	349(41)	336(54)	323·5(56)	314(52)	—	3
		—	354	338	324	313	—	10
20	D-Homoandrosta-4 : 9 (11) : 16-trien-3-one	368 [a] (17)	350(33)	338(43)	326(42)	314 [a] (35)	—	3
21	Cholest-5-en-7-one	—	345 [a] (29)	334(32)	322 [a] (28)	—	—	3
22	3β-Acetoxycholest-5-en-7-one	—	350 [a] (13)	337(17)	325 [a] (13)	—	—	3
23	3β-Acetoxylanost-5-en-7-one	380 [a] (19)	364(38)	350(47)	339(44)	—	—	3
24	3β-Acetoxyergosta-7 : 22-dien-6-one	360(24)	345(53)	332(68)	320(67)	310·5(59)	—	3
25	3β-Acetoxy-23-bromo-5α : 22*a*-spirost-9(11)-en-12-one	369(7)	350(18)	337·5(24)	327(23)	—	—	3
26	11-Oxo-β-amyrin acetate	374(9)	355(18·5)	345(22)	335(22)	—	—	3
27	11-Oxo-18-*iso*-β-amyrin acetate	*ca.* 370 [a] (29)	*ca.* 351 [a] (64)	340(80)	329(82)	—	—	3
28	11-Oxo-α-amyrin acetate	374 [a] (11)	357(26)	345(34·5)	335(34)	—	—	3

TABLE 6. 2 : 3-*Disubstituted* cyclo*hex-2-enones.*

No.	Substance	A	B	C	D	E	F	Ref.
29	1 : 14-Dimethyl-2 : 8-dioxo-$\Delta^{(11)}$-dodecahydrophanthrene	351(26)	336(41)	322(50)	308(54)	297(53)	—	3
30	$\Delta^{(11)}$-Dodecahydro-1 : 14-dimethyl-6β : 7β-*iso*propylidenedioxyphenanthrene	349(41)	336(55)	324(57)	—	—	—	3
31	3β-Acetoxyergosta-8(9) : 22-dien-7-one	—	—	*332(36)*	—	*304(33)*	—	3
32	3β-Acetoxyergosta-8(9) : 22-dien-11-one	—	—	*327(51)*	—	*306(48)*	—	3
33	Methyl 3β-acetoxy-4 : 4 : 14α-trimethyl-11-oxochol-8(9)-enoate	—	353(29)	342·5(31)	—	322 [a] (24)	—	3

TABLE 7. *Derivatives of* 2-*methylene*cyclo*hexanone.*

No.	Substance	A	B	C	D	E	F	Ref.
34	Pulegone	—	—	*329*	—	—	—	10
35	3β-Acetoxycholest-8(14)-en-7-one	—	—	*329(63)*	—	—	—	3
36	Methyl 3β-acetoxy-19-oxo-olean-13(18)-en-28-oate	—	—	*324(104)*	—	—	—	3

Turning now to the degree of fine structure exhibited by the various ketones, we can observe in the examples tabulated the complete range from a smooth curve with no detectable fine structure through intermediate degrees to a complex band showing up to eight well-resolved subsidiary maxima. Acraldehyde (No. 9), the simplest substance, shows well-defined vibrational structure; α-methylacraldehyde (No. 10) shows less and β-methylacraldehyde (No. 11) almost none; acylic unsaturated ketones and derivatives of 2-methylene*cyclo*hexanone show no detectable fine structure. There is a striking and rather unexpected contrast between the 5-en-7-ones of the cholestane (Nos. 21 and 22) and lanostane (No. 23) series, the former showing only a trace of fine structure, the latter having bands A to D well developed and shifted to abnormally long wavelengths. The spectra of the 12-en-11-ones of the α- and β-amyrin series are very similar, consisting of a rather weak band with sub-maxima A to D well resolved: the spectrum of the 18α-epimer of the β-amyrin series is quite different, consisting of a more intense band with only faint indications of fine structure.

The approximately constant separation between successive vibrational bands of about 1000—1200 cm.$^{-1}$ probably corresponds roughly with the strongest band progression of 1260 cm.$^{-1}$ in the vapour spectrum of acraldehyde (Lüthy, *Z. phys. Chem.*, 1923, **107**, 285). Since this is probably the CO stretching frequency in the excited state of the ketones, analysis of the fine structure of the spectra offers, in principle, a means of investigating the influence

TABLE 8. *Derivatives of* 2-*methylene*cyclo*pentanone.*

No.	A	B	C	D	E	F	G	H	Ref.
37	3β-Acetoxycholest-8(14)-en-15-one								
	389(22)	369(54)	356(69)	342·5(61·5)	328* (45)	—	303* (57)	291(66)	3
38	3β-Hydroxy-22*a* : 5α-c-nor : D-homospirost-13(17*a*)-en-11-one								
	385(36)	368(59)	354(69)	340(61)	324(45)	313(37)	—	288* (34)	3

Refs.: 1, French and Wiley, *J. Amer. Chem. Soc.*, 1949, **71**, 3702. 2, Ross, *J.*, 1945, **25**. 3, This paper. 4, Halsall, Meakins, and Swayne, *J.*, 1953, 4139. 5, Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013. 6, Fried and Klingsberg, *ibid.*, 1953, **75**, 4929. 7, Wintersteiner and Moore, *ibid.*, p. 4938. 8, Lüthy, *Z. phys. Chem.*, 1923, **107**, 285. 9, Saksena and Kagarise, *J. Chem. Phys.*, 1951, **19**, 994. 10, Mohler, *Helv. Chim. Acta*, 1937, **20**, 289.

of ring size and molecular structure on the excited-state frequencies to match the detailed knowledge of the ground-state frequencies recently gained from infrared and Raman spectra. It may be significant that the most highly developed fine structure is shown by the most rigid molecules, the 2-alkylidene*cyclo*pentanones (cf. Lewis and Calvin, *Chem. Rev.*, 1939, **25**, 318; Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127).

EXPERIMENTAL

Absorption spectra were measured at room temperature as described previously (*J.*, 1954, 282) in 1-cm. or 4-cm. silica cells, according to the solubility of the ketone in *n*-hexane, which was B.D.H. "Special for Spectroscopy."

Liquids were fractionally distilled just before use and had b. p.s and refractive indices very close to the recorded values. Solids were purified by recrystallisation, preceded when necessary by chromatography. Their purity was checked by m. p. and/or rotation. The intense absorption bands of all the ketones had the expected wavelengths and intensities. In most cases, including all that showed poorly resolved fine structure, the spectrum was remeasured after further purification, with very similar results.

This investigation was made possible by the generosity of Professor D. H. R. Barton, F.R.S., in putting his collection of terpenoid and steroid samples at our disposal. We are also most grateful to the following for their kindness in supplying valuable samples: Dr. J. Elks (Glaxo Laboratories Ltd., Greenford) (Nos. 25 and 31); Dr. R. F. Hirschmann (Merck & Co. Inc., Rahway) (No. 38); Dr. K. Miescher (Ciba Ltd., Basle) (No. 29); Dr. Ch. Tamm (University of Basle) (No. 15); Dr. O. J. Weinkauff (Monsanto Chemical Co., St. Louis) (Nos. 12, 20, and 30).

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Nitramines and Nitramides. Part VIII. Additional Measurements of the Rate of Decomposition of Primary Nitramines, and the Evidence for General Acid-catalysis.*

By I. N. Denton and Alex. H. Lamberton.

(Reprint Order No. 6039.)

Published measurements of rates of decomposition of the compounds $R{\cdot}NH{\cdot}NO_2$ by aqueous acids have now been extended to the cases where R = EtMeCH, $EtMeCH{\cdot}CH_2$, or $Me_3C{\cdot}CH_2$. These decomposed more readily than the simpler alkyl nitramines, and exhibited significant differences between sulphuric and hydrochloric acid solutions of the same hydrogen-ion content. By using *iso*propylnitramine, bisulphate ions have been shown to be catalysts in their own right: other (un-ionised) acids may also act as catalysts, but are too feeble for their influence to be determined with precision.

In Part IV (*J.*, 1953, 1998) it was shown that, for R = Me, Et, Pr^i, or Bu^t, the rate of decomposition of $R{\cdot}NH{\cdot}NO_2$ by aqueous acids was proportional to $[H^+][R{\cdot}NH{\cdot}NO_2]$. Electron-donation by R seemed to favour decomposition, though *tert.*-butylnitramine was anomalous; and we have therefore prepared and examined *sec.*-butyl-, 2-methylbutyl-, and *neo*pentyl-nitramine. As expected, these decompose more rapidly than the analogues previously investigated; for the complete series the relative rates are $R = Me_3C{\cdot}CH_2 > EtMeCH > EtMeCH{\cdot}CH_2 > Pr^i > Et$ or $Bu^t > Me > CH_2{\cdot}CO_2H$. The ready decomposition of *neo*pentylnitramine and additional evidence, as yet unpublished, show that our formulation of the rate-determining step as $R{\cdot}NH{\cdot}NO_2 + H^+ \longrightarrow R^+ + NH_2{\cdot}NO_2$ is correct as far as the production of alkyl cations is concerned; but the suggestion that nitramine (as such) is set free was possibly overhasty, and is under experimental examination.

The rates of decomposition were determined by the acidimetric technique (Part IV, *loc. cit.*) and are given in Table 1, which is directly comparable with Table 1 of Part IV.

Table 1. *Decomposition of the nitramines,* $R{\cdot}NH{\cdot}NO_2$, *initially* 0·05M *in aqueous acids, at* 85° ± 0·2°.

1 Run no.	2 R	3 Acid (mole/l. at 20°)	4 First-order rate coeff., 10^5k (min.$^{-1}$)	5 Second-order rate coeff., 10^5k (l. mole^{-1} min.$^{-1}$)
I	MeEtCH	HCl, 0·0514	3·9	78
II	,,	H_2SO_4, 0·0536	5·1	96
III	,,	,, 0·0269	2·6	95
IV	$MeEtCH{\cdot}CH_2$	,, 0·0266	2·3	85
V	$Me_3C{\cdot}CH_2$	HCl, 0·0487	4·9	104
VI	,,	,, 0·0249	2·5	103
VII	,,	H_2SO_4, 0·0535	6·3	119
VIII	,,	,, 0·0266	3·1	114

Values in column 5 are those of column 4, divided by the appropriate value of $[H^+]$.

The values of the second-order rate coefficients found for solutions in sulphuric acid seemed to differ significantly from those determined in hydrochloric acid, even when allowance was made for imprecision in the calculation of the hydrogen-ion content of sulphuric acid solutions at 85°. This anomaly could be removed by assuming (1) that the second-order coefficients in hydrochloric acid are the true catalytic constants of the hydrogen ion; and (2) that the observed first-order rates in sulphuric acid are given by $k_{H^+}[H^+] + k_{HSO_4^-}[HSO_4^-]$, where the catalytic constant of the bisulphate ion is of the order of one-tenth of that of the hydrogen ion. We have therefore sought evidence of general acid-catalysis in the case of *iso*propylnitramine, where, from our previous work, k_{H^+} is about 60×10^{-3} l. mole^{-1} min.$^{-1}$.

In our investigation of general acid-catalysis we reverted to the manometric technique (Part IV, *loc. cit.*), since acidimetry was inapplicable. The decompositions were slow,

* Part VII, *J.*, 1954, 2391.

and we were forced to use unduly large concentrations of catalyst: salt effects of unknown extent made it unwise to place too much reliance on individual values. It certainly appears that bisulphate ions have a catalytic action: thus solutions of *iso*propylnitramine (0·05M) in sodium hydrogen sulphate (0·500 and 1·000M at 20°) gave first-order rate coefficients of 7·4 and 13·4 $\times$ 10^{-3} min.$^{-1}$ respectively; on the basis of hydrogen-ion content alone the rates would have been about 1·2 and 1·6 $\times$ 10^{-3} min.$^{-1}$.

We examined the decomposition in sodium hydrogen sulphate buffers of constant ratio ($NaHSO_4 : Na_2SO_4 = 1 : 1$), using sodium chloride to compensate, to some extent, for changes in salt concentration. The results are given in Table 2. In runs XII, XIII, and XVI, $[Na^+]$ was kept constant, whilst in runs XI, XV, and XIX the total ionic strength was maintained. It appears that, though changes in salt concentration alter the rate (compare runs XVI, XVII, and XVIII), such alterations are small compared with those proportional to the bisulphate content, and no point is far distant from a line giving an intercept of 1·7 $\times$ 10^{-3} min.$^{-1}$—of the right order for the hydrogen-ion concentration of these buffers—and a catalytic constant of 8·2 $\times$ 10^{-3} l. mole^{-1} min.$^{-1}$ for the bisulphate ion.

TABLE 2. *Decomposition of* iso*propylnitramine, initially* 0·05M, *in sodium hydrogen sulphate buffer solutions at* 85° ± 0·2°.

Run no.	Components (mole/l. at 20°) $NaHSO_4$ and Na_2SO_4	NaCl	First-order rate coeff., 10^3k (min.$^{-1}$)	Divergence from line $v = 1·7 + 8·2[HSO_4^-]$ (in units of 10^3k, min.$^{-1}$)
XI	1·027	Nil	9·9	−0·2
XII	1·007	Nil	10·2	+0·3
XIII	0·772	0·831	7·3	−0·7
XIV	0·749	0·548	7·9	+0·1
XV	0·619	1·700	7·8	+1·0
XVI	0·385	1·956	4·5	−0·4
XVII	0·380	0·756	4·3	−0·5
XVIII	0·379	2·957	5·0	+0·2
XIX	0·300	2·900	4·8	+0·6

We have also examined the behaviour of *iso*propylnitramine in phosphoric acid, and in phosphate, acetate, and chloroacetate buffers. The results are given in Table 3. In all cases the observed rates are greater than those calculated for the influence of hydrogen ions alone; though positive salt effects may account for part of the increase, they can hardly produce the more than ten-fold increases shown in the buffered solutions.

TABLE 3. *Decomposition of* iso*propylnitramine, initially* 0·05M, *in phosphoric, acetic, and chloroacetic acid solutions at* 85° ± 0·2°.

Run no.	Composition of solutions, at 20°	Calc. value of $10^3[H^+]$ (at 85°)	First-order rate coefficient 10^3k (min.$^{-1}$) Observed	Calc. for $[H^+]$ alone
XX	1·0M-H_3PO_4	50	17·4	3·0
XXI	0·5M-H_3PO_4	34	9·9	2·0
XXII	0·49M-H_3PO_4, and 0·49M-NaH_2PO_4	2·7	5·3	0·16
XXIII	0·25M-H_3PO_4, 0·25M-NaH_2PO_4, and 0·25M-NaCl	2·7	3·1	0·16
XXIV	1·0M-NaH_2PO_4	0·22	0·2	0·013
XXV	1·0M-$CH_3{\cdot}CO_2H$, and 1·0M-$CH_3{\cdot}CO_2Na$	0·01	0·2	0·0006
XXVI	0·97M-$CH_2Cl{\cdot}CO_2H$, and 0·97M-$CH_2Cl{\cdot}CO_2Na$	0·6	1·8	0·035

A buffer of composition 0·5M-NaH_2PO_4 and 0·5M-Na_2HPO_4 gave no observable decomposition at 85°.

We therefore consider that the reaction exhibits general acid-catalysis: in particular, for *iso*propylnitramine at 85°, the catalytic constants [in units of 10^{-3} l. mole^{-1} min.$^{-1}$] are about 60 for H^+, 8 for HSO_4^-, and perhaps of the order of 10 for H_3PO_4, 2 for $CH_2{\cdot}ClCO_2H$, and 0·2 for $CH_3{\cdot}CO_2H$.

EXPERIMENTAL

Reaction rates were evaluated on the basis of natural logarithms. The techniques of measurement have been described in an earlier paper of this series (Part IV, *J.*, **1953**, 1998). In calculating hydrogen-ion concentrations at 85° use was made of the work of Hamer (*J.*

Amer. Chem. Soc., **1934**, **56**, 860), of Harned and Embree (*ibid.*, p. 1050), and of Nims (*ibid.*, p. 1110). *sec.*-Butylnitramine (van Erp, *Rec. Trav. chim.*, 1895, **14**, 31) was prepared from *sec.*-butylnitrourethane [obtained from *sec.*-butylamine by the general method of Curry and Mason (*J. Amer. Chem. Soc.*, 1951, **73**, 5043)] and purified by distillation at 76°/0·75 mm. (Found: equiv., 119. Calc. for $C_4H_{10}O_2N_2$: equiv., 118).

2-*Methylbutylnitramine*.—Ethyl β-methylvalerate (25 g.) (prepared from *sec.*-butylmalonic ester by hydrolysis, decarboxylation, and esterification) was refluxed for 40 hr. with hydrazine hydrate (15 ml.) in ethanol. After removal of the ethanol by distillation the hydrazide was dissolved in an excess of 2N-hydrochloric acid, ether (125 ml.) added, and sodium nitrite (14·5 g. in 30 ml. of water) run in, with stirring, at <10°. The ether layer was separated, the aqueous layer was re-extracted with ether, and the combined extracts were washed with sodium hydrogen carbonate and dried ($CaCl_2$). Ethanol (80 ml.) was added to this solution of the azide and the residue, after removal of the ether through a fractionation column, was refluxed for 6 hr. Distillation, under reduced pressure, removed excess of ethanol and yielded fractions of b. p. 86—89°/2 mm. and 101—102°/4 mm. The second fraction on redistillation gave N-(2-*methylbutyl*)*urethane* (2·5 g.; b. p. 108—109°/7 mm.) (Found: C, 59·9; H, 10·5. $C_8H_{17}O_2N$ requires C, 60·4; H, 10·7%). On nitration by Curry and Mason's method (*loc. cit.*) the corresponding nitrourethane (3 g., crude) was obtained: passage of ammonia through an ethereal solution of the nitrourethane yielded the ammonium salt of the nitramine, which was collected and decomposed with 2N-hydrochloric acid. Ether-extraction and distillation (98—99°/0·7 mm.), followed by sublimation at 85°/16 mm., yielded 2-*methylbutylnitramine* (1·5 g.) as small flakes of m. p. 32° (Found: C, 45·5; H, 9·2%; equiv., 133. $C_5H_{12}O_2N_2$ requires C, 45·5; H, 9·1%; equiv., 132).

neo*Pentylnitramine*.—*neo*Pentylamine (Walter and McElvain, *J. Amer. Chem. Soc.*, **1934**, **56**, 1614) was prepared from trimethylacetic acid by way of the chloride, amide, and nitrile. Treatment by Curry and Mason's method (*loc. cit.*) gave successively the (crude) urethane and nitrourethane in almost quantitative yields. neo*Pentylnitramine*, prepared from the nitrourethane as described in the preceding paragraph, was purified by distillation (92—93°/2·5 mm., 76—77°/0·5 mm.) and was solid at temperatures below 16° (Found: C, 45·0; H, 9·1%; equiv., 133. $C_5H_{12}O_2N_2$ requires C, 45·5; H, 9·1%; equiv., 132).

STAVELEY CHEMICAL LABORATORIES,
THE UNIVERSITY, SHEFFIELD, 10.

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The Chemistry of the Pyrrocolines. Part VIII. Alkyl Derivatives.*

By D. O. HOLLAND and J. H. C. NAYLER.

[Reprint Order No. 6042.]

Several alkylpyrrocolines have been prepared and their reactions with methyl and ethyl iodide studied. Complete substitution in the 5-membered ring can lead to both 1 : 1 : 2 : 3- and 1 : 2 : 3 : 3-tetra-alkylpyrrocolinium iodides, which may be distinguished by their ultraviolet absorption spectra.

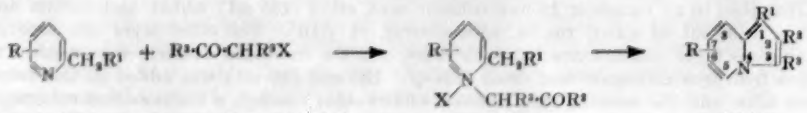
THE most useful method for the preparation of 2-substituted pyrrocolines is that of Tschitschibabin (*Ber.*, 1927, **60**, 1607) in which the adduct (II) from a suitably substituted pyridine (I) and an α-halogeno-ketone is treated with a base, usually hot sodium hydrogen carbonate solution. Since many simple pyrrocolines are unstable in air it is often convenient to prepare the intermediate (II) in bulk and convert it into the pyrrocoline (III) as required.

The reaction of bromo-ketones with pyridines is often vigorous (cf. Holliman and Schickerling, *J.*, 1951, 914) but can be moderated by diluting the mixture with acetone. With this modification 2-methyl-, 1 : 2-dimethyl-, and 2 : 3-dimethyl-pyrrocoline were prepared in appreciably improved yields, and a good yield of 2 : 7-dimethylpyrrocoline was also obtained. No diluent was required in the first stage of the syntheses of 1 : 2 : 3-trimethyl- and 3-benzyl-2-methyl-pyrrocoline. No more than 5% of 2 : 5-dimethylpyrrocoline could be obtained from 2 : 6-lutidine and bromo- or chloro-acetone, but poor

* Part VII, *J.*, 1955, 1504.

yields appear to be not unusual in the synthesis of 5-substituted pyrrocolines (cf. Tschitschibabin, *loc cit.*; Buu-Hoï and Khoi, *Compt. rend.*, 1950, **230**, 967). Stable chloroplatinates were readily obtained from most of the pyrrocolines, and chloroplatinates also proved useful for the characterisation of the quaternary intermediates (II) in those cases where the pure bromides were not isolated.

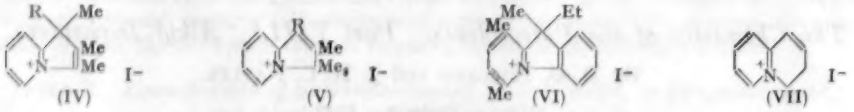
The 2-ethylpyridine required for the preparation of 1 : 2-dimethyl- and 1 : 2 : 3-trimethyl-pyrrocolines was prepared by Wolff–Kishner reduction of 2-acetylpyridine



(I) (X = Cl or Br) (II) (III)

(Prostenik and Balling, *Arkiv Kemi*, 1946, **18**, 11). The Clemmensen procedure, by which Furst (*J. Amer. Chem. Soc.*, 1949, **71**, 3550) obtained 2-ethylpyridine in about 80% yield, in our hands gave only 1-2′-pyridylethanol. Späth and Galinovsky (*Ber.*, 1938, **71**, 721) similarly obtained an alcohol from 3 : 5-dimethyl-2-propionylpyridine. 1-2′-Pyridylethanol gave a crystalline hydrogen phthalate and an oily phenylurethane, but the picrate of the latter, like that of the parent alcohol, was crystalline. We confirm that 1-2′-pyridylethanol has the physical properties recently recorded by Bullitt and Maynard (*J. Amer. Chem. Soc.*, 1954, **76**, 1370) and agree with their conclusion that the solid described by Pinner (*Ber.*, 1901, **34**, 4241) cannot have been this alcohol.

Alkylation of pyrrocolines was first reported by Scholtz (*Ber.*, 1912, **45**, 1718; *Arch. Pharm.*, 1913, **251**, 666) who obtained methiodides of di- and tri-methylpyrrocolines by the action of methyl iodide at 120° on pyrrocoline and 7-methylpyrrocoline respectively. Rossiter and Saxton (*J.*, 1953, 3654) prepared another trimethylpyrrocoline methiodide, m. p. 197·5°, together with a trace of 1 : 2 : 3-trimethylpyrrocoline, by heating 2-methylpyrrocoline with methyl iodide. Under essentially similar conditions we obtained a product, m. p. 180—181°, which also arose by the action of methyl iodide on 1 : 2 : 3-trimethylpyrrocoline at room temperature.



(IV) (V) (VI) (VII)

Saxton (*J.*, 1951, 3239) adduced evidence that 1 : 3 : 5 : 7-tetramethylpyrrocoline methiodide contained a *C*-alkylated cation of the pyridinium type. Possible structures of such a type for 1 : 2 : 3-trimethylpyrrocoline methiodide are (IV and V; R = Me), but no decision can be made between these alternatives on chemical grounds. However, the elegant experiments of Robinson and Saxton (*J.*, 1952, 976), in which the ethiodide of 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline was shown to be identical with the methiodide of 1-ethyl-5 : 8-dimethyl-2 : 3-benzopyrrocoline, both having structure (VI), suggested a possible means of establishing the structures of 1 : 2 : 3-trialkylpyrrocoline alkiodides in which the alkyl substituents were not all alike.

Heating 1 : 2 : 3-trimethylpyrrocoline with ethyl iodide under pressure apparently gave a mixture of isomers, $C_{12}H_{18}NI$, which after many crystallisations afforded one pure component, m. p. 199—200°. The same compound was obtained from 1-ethyl-2 : 3-dimethylpyrrocoline and methyl iodide and is therefore formulated as 1-ethyl-1 : 2 : 3-trimethylpyrrocolinium iodide (IV; R = Et), whilst an isomer which accompanied it in larger amount in the methylation is regarded as 1-ethyl-2 : 3 : 3-trimethylpyrrocolinium iodide (V; R = Et). These two isomers exhibited markedly different ultraviolet absorption (see Fig. 1), whilst further evidence for the presence of the 1 : 2-double bond in the isomer (V; R = Et) is afforded by the similarity of its spectrum to that of the pyridocolinium iodide (VII) (Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832). The only pure

product which could be isolated from the reaction of 3-ethyl-2-methylpyrrocoline with an excess of methyl iodide was formulated as 3-ethyl-1 : 2 : 3-trimethylpyrrocolinium iodide because of the resemblance of its spectrum to that of the iodide (V; R = Et) (see Fig. 1).

The methiodide, m. p. 180—181°, of 1 : 2 : 3-trimethylpyrrocoline exhibited ultraviolet absorption of a type intermediate between those of 1 : 1 : 2 : 3- and 1 : 2 : 3 : 3-tetraalkylpyrrocolinium iodides. It was probably a mixture or molecular compound of (IV and V; R = Me), whilst the form, m. p. 197·5°, the isolation of which by Rossiter and Saxton (*loc. cit.*) we have been unable to repeat, may have been one of the pure components. An " intermediate " type of absorption was also shown by an incompletely purified product from 1 : 2 : 3-trimethylpyrrocoline and ethyl iodide, in which 1-ethyl-1 : 2 : 3-trimethyl-

FIG. 1. FIG. 2.

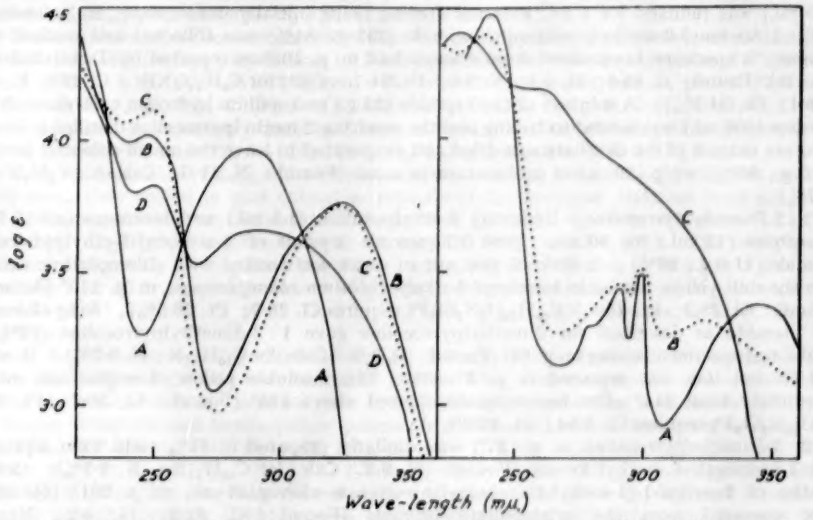
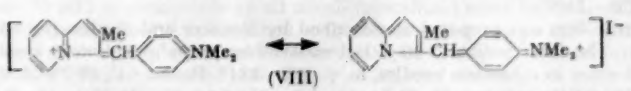


FIG. 1. *Absorption spectra of* (A) 1-*ethyl*-1 : 2 : 3-, (B) 1-*ethyl*-2 : 3 : 3-, *and* (C) 3-*ethyl*-1 : 2 : 3-*trimethylpyrrocolinium iodide, and* (D) 1 : 2 : 3-*trimethylpyrrocoline methiodide, m. p.* 180—181°, *all in* EtOH.

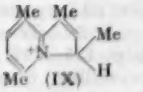
FIG. 2. *Absorption spectra of* (A) 2-*methylpyrrocoline in ethanol,* (B) 2-*methylpyrrocoline hydriodide in ethanol, and* (C) 2-*methylpyrrocoline hydriodide in ethanolic* 0·08N-HCl.

pyrrocolinium iodide (V; R = Et) was probably accompanied by some of the 3-ethyl compound.

Rossiter and Saxton (*loc. cit.*) have reported that the crystals which separate when 2-methylpyrrocoline is kept in methyl iodide at room temperature are 2-methylpyrrocoline hydriodide, the methylation product apparently remaining in solution as the free base. We obtained the same hydriodide, m. p. 169—172° (decomp.), by the action of either ethyl iodide or hydriodic acid on 2-methylpyrrocoline. Deposition of the corresponding hydriodides, rather than the methiodides, was also observed when 1 : 2-, 2 : 5-, and 2 : 7-dimethylpyrrocolines were kept with methyl iodide. Treatment of 2-methylpyrrocoline hydriodide with *p*-dimethylaminobenzaldehyde gave a deep blue dye, presumably (VIII) or the



(VIII)



(IX)

1-substituted isomer. Other pyrrocolines containing free 1- or 3-positions also gave intense blue or violet Ehrlich colours with *p*-dimethylaminobenzaldehyde in the presence of mineral acid (cf. Clemo, Fox, and Raper, *J.*, 1953, 4173).

The striking similarity of the spectrum recorded by Saxton (*loc. cit.*) for 1 : 3 : 5 : 8-tetramethylpyrrocoline in ethanolic hydrochloric acid to those of the 1 : 2 : 3 : 3-tetra-alkylpyrrocolinium iodides indicates (IX) as the probable structure of the 1 : 3 : 5 : 8-tetramethylpyrrocolinium ion. On the other hand, the spectrum of 2-methylpyrrocoline hydriodide in ethanol chiefly resembled that of 2-methylpyrrocoline itself (see Fig. 2), owing no doubt to dissociation. Inclusion of a large excess of hydrogen chloride radically altered the absorption curve, but there was still no resemblance to the spectra of either the 1 : 1 : 2 : 3- or the 1 : 2 : 3 : 3-tetra-alkylpyrrocolinium iodides, so that the 2-methylpyrrocolinium ion was presumably not a single species.

Experimental

2-Methylpyrrocoline.—A mixture of α-picoline (120 ml.) and bromoacetone (167 g.) in acetone (200 ml.) was refluxed for 1 hr., external heating being initially unnecessary, and allowed to cool. 1-Acetonyl-2-methylpyridinium bromide (237 g., 84%) was collected and washed with acetone; a specimen crystallised from ethanol had m. p. 196° as reported by Tschitschibabin (*loc. cit.*) (Found : C, 46·6; H, 5·1; N, 6·0; Br, 34·7. Calc. for $C_9H_{12}ONBr$: C, 47·0; H, 5·3; N, 6·1; Br, 34·7%). A solution of the bromide (23 g.) and sodium hydrogen carbonate (20 g.) in water (500 ml.) was heated to boiling and the resulting 2-methylpyrrocoline distilled in steam. An ether extract of the distillate was dried and evaporated to leave the cream-coloured product (12·5 g., 95%), m. p. 59° after sublimation *in vacuo* (Found : N, 11·0. Calc. for C_9H_9N : N, 10·7%).

1 : 2-*Dimethylpyrrocoline.*—Refluxing 2-ethylpyridine (6·5 ml.) and bromoacetone (7·7 g.) in acetone (12 ml.) for 90 min. gave deliquescent crystals of 1-acetonyl-2-ethylpyridinium bromide (11·0 g., 80%). A little of this salt in water was treated with chloroplatinic acid to give the dull yellow insoluble *1-acetonyl-2-ethylpyridinium chloroplatinate*, m. p. 210° (decomp.) (Found : Cl, 28·2; Pt, 26·5. $C_{20}H_{26}O_2N_2Cl_6Pt$ requires Cl, 28·9; Pt, 26·5%). Ring-closure of the bromide as described for 2-methylpyrrocoline gave 1 : 2-dimethylpyrrocoline (92%), a resublimed specimen having m. p. 63° (Found : N, 9·9. Calc. for $C_{10}H_{11}N$: N, 9·7%). Rossiter and Saxton (*loc. cit.*) reported m. p. 57—58°. The insoluble yellow *chloroplatinate* melted indefinitely from 214° after becoming discoloured above 175° (Found : Cl, 30·7; Pt, 28·1. $C_{20}H_{24}N_2Cl_6Pt$ requires Cl, 30·4; Pt, 27·9%).

2 : 3-*Dimethylpyrrocoline*, m. p. 37°, was similarly prepared in 61% yield from α-picoline and 1-bromoethyl methyl ketone (Found : N, 9·5. Calc. for $C_{10}H_{11}N$: N, 9·7%). Orange needles of *2-methyl-1-(1-methyl-2-oxopropyl)pyridinium chloroplatinate*, m. p. 201° (decomp.), were prepared from the intermediate bromide (Found : C, 32·2; H, 4·2; N, 4·1. $C_{20}H_{26}O_2N_2Cl_6Pt$ requires, C, 32·6; H, 3·8; N, 3·8%).

2 : 7-*Dimethylpyrrocoline.*—A solution of 2 : 4-lutidine (27·3 ml.) and bromoacetone (33·3 g.) in acetone (50 ml.) was refluxed for 15 min., a heavy oil separating, and set aside overnight. After removal of acetone *in vacuo* the frothy residue was dissolved in water and the solution was clarified by ether-extraction. Addition of chloroplatinic acid to a little of the aqueous phase gave pale orange microcrystals of *1-acetonyl-2 : 4-dimethylpyridinium chloroplatinate*, m. p. 219—220° (decomp.) (Found : C, 32·6; H, 4·1; Pt, 26·6. $C_{20}H_{26}O_2N_2Cl_6Pt$ requires C, 32·6; H, 3·8; Pt, 26·5%). The bulk of the aqueous solution was diluted to about 600 ml., treated with sodium hydrogen carbonate (60 g.), and distilled. 2 : 7-*Dimethylpyrrocoline* (24·4 g., 70%) was isolated from the steam-distillate in the usual way and after vacuum-sublimation formed colourless plates, m. p. 78—79°, which became black within 36 hr. (Found : N, 9·3. $C_{10}H_{11}N$ requires N, 9·7%). The orange-yellow *chloroplatinate* decomposed above 200° (Found : C, 34·2; H, 3·0; Pt, 28·2. $C_{20}H_{24}N_2Cl_6Pt$ requires C, 34·3; H, 3·4; Pt, 27·9%).

2 : 5-*Dimethylpyrrocoline.*—A solution of 2 : 6-lutidine (44 ml.) and bromoacetone (52·5 g.) in acetone (60 ml.) was refluxed for 30 min. and worked up as described for 2 : 7-dimethylpyrrocoline, to give 2 : 5-dimethylpyrrocoline (2·72 g.), b. p. 116—117°/14 mm. Tschitschibabin (*loc. cit.*) reported b. p. 238—240°.

1 : 2 : 3-Trimethylpyrrocoline was prepared as described by Rossiter and Saxton (*loc. cit.*), b. p. 135—137°/13 mm. The intermediate *2-ethyl-1-(1-methyl-2-oxopropyl)pyridinium bromide* crystallised from ethanol–ether in colourless needles, m. p. 182—184° (Found : C, 50·7; H, 6·2; N, 5·5; Br, 31·2. $C_{11}H_{16}ONBr$ requires C, 51·1; H, 6·2; N, 5·4; Br, 31·0%). 1 : 2 : 3-*Trimethylpyrrocoline chloroplatinate*, a pale yellow microcrystalline powder, had m. p. 179° (decomp.) (Found : N, 4·1; Cl, 29·8; Pt, 26·7. $C_{22}H_{28}N_2Cl_6Pt$ requires N, 3·9; Cl, 29·2; Pt, 26·8%).

3-Benzyl-2-methylpyrrocoline.—α-Picoline (8·9 ml.) and 1-bromo-2-phenylethyl methyl ketone (Janetzky and Verkade, *Rec. Trav. chim.*, 1945, **64**, 129) (20·5 g.) were heated on the steam-bath for 8 hr., then cooled and diluted with water. Sodium hydrogen carbonate was added to pH 7 and the solution was clarified by extraction with chloroform. A small portion of the aqueous solution was acidified with hydrochloric acid and treated with chloroplatinic acid to give a cream-coloured precipitate of 1-(*1-benzyl-2-oxopropyl*)-*2-methylpyridinium chloroplatinate*, decomp. >170° (Found: N, 3·2; Cl, 24·2; Pt, 21·7. $C_{32}H_{36}O_2N_2Cl_6Pt$ requires N, 3·2; Cl, 23·9; Pt, 22·0%). The bulk of the aqueous solution was treated with a further 16 g. of sodium hydrogen carbonate and refluxed for 4 hr., then cooled and extracted with chloroform. Evaporation of the dried extracts gave *3-benzyl-2-methylpyrrocoline* as a crude brown powder (5·06 g.) which was best purified by sublimation at 0·05 mm. (bath, 80—120°), giving colourless crystals, m. p. 93—94° (Found: C, 87·1; H, 6·9; N, 6·2. $C_{16}H_{15}N$ requires C, 86·8; H, 6·8; N, 6·3%). The *chloroplatinate* had m. p. 178—179° (decomp.) (Found: N, 3·2; Cl, 25·0; Pt, 22·8. $C_{32}H_{32}N_2Cl_6Pt$ requires N, 3·3; Cl, 25·0; Pt, 22·9%).

1-2′-Pyridylethanol.—Clemmensen reduction of 2-acetylpyridine was carried out as described by Furst (*loc. cit.*) for the preparation of 2-ethylpyridine, but the product was 1-2′-pyridylethanol (67%), b. p. 204—211°/754 mm. A redistilled specimen had b. p. 207°/747 mm. (Found: C, 68·0; H, 7·7; N, 11·0. Calc. for C_7H_9ON: C, 68·3; H, 7·4; N, 11·4%). The *picrate*, prepared in benzene, crystallised from a little ethyl acetate as yellow prisms, m. p. 85—86° (Found: C, 44·4; H, 3·4; N, 15·8. $C_{13}H_{12}O_8N_4$ requires C, 44·3; H, 3·4; N, 15·9%). A solution of the alcohol (3·4 g.) and phthalic anhydride (4·1 g.) in acetone (15 ml.) was refluxed for 90 min., then cooled to give colourless crystals of the *hydrogen phthalate* (4·42 g.), m. p. 134—136° after further crystallisation from acetone (Found: C, 66·6; H, 5·0; N, 5·0%; equiv., 268. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%; equiv., 271). The oily phenylurethane, obtained by heating the alcohol (1 g.) with phenyl *iso*cyanate (0·96 g.) in dry toluene under reflux for 30 hr., gave a *picrate* (2·84 g.) which crystallised from ethanol in yellow prisms, m. p. 164—166° (Found: C, 51·0; H, 3·7; N, 14·8. $C_{20}H_{17}O_9N_5$ requires C, 51·0; H, 3·6; N, 14·9%).

1 : 2 : 3-Trimethylpyrrocoline Methiodide.—(*a*) 2-Methylpyrrocoline (3·1 g.), methyl iodide (6 ml.), and methanol (10 ml.) were heated at 120° for 7 hr., then evaporated *in vacuo*. Trituration of the residue with dry acetone gave 1 : 2 : 3-trimethylpyrrocoline methiodide (4·83 g. in two crops), which formed lemon-yellow prisms (from ethanol) or needles (from *iso*propanol), m. p. 180—181° (Found: C, 48·1; H, 5·3; N, 4·9; I, 41·8. Calc. for $C_{12}H_{16}NI$: C, 47·9; H, 5·4; N, 4·7; I, 42·1%). (*b*) 1 : 2 : 3-Trimethylpyrrocoline (3·7 g.) was kept in methyl iodide (15 ml.) for 1 week, then diluted with dry ether. The dark supernatant liquid was decanted and the crystals (2·73 g.) were washed successively with ether and acetone, then crystallised from ethanol or *iso*propanol; they had m. p. 180—181° alone or mixed with the product from (*a*).

1 : 2 : 3-Trimethylpyrrocoline Ethiodide.—1 : 2 : 3-Trimethylpyrrocoline (3·8 g.), ethyl iodide (10 ml.), and ethanol (10 ml.) were heated at 120° for 8 hr. Crystals separated from the strongly cooled solution, and further crops were obtained by evaporating the filtrate and triturating the residue with acetone. Recrystallisation from acetone–ether to constant m. p. gave the mixed isomers of the ethiodide as cream-coloured crystals (2·4 g.), m. p. 179—180° (Found: C, 49·7; H, 6·2; N, 4·2. Calc. for $C_{13}H_{18}NI$: C, 49·5; H, 5·8; N, 4·4%). Three crystallisations from ethanol followed by ten from *iso*propanol gave *1-ethyl-1 : 2 : 3-trimethylpyrrocolinium iodide* (0·26 g.) as cream-coloured needles, m. p. 199—200° (Found: C, 49·8; H, 6·2; N, 4·3%).

Reaction of 1-Ethyl-2 : 3-dimethylpyrrocoline with Methyl Iodide.—1-Ethyl-2 : 3-dimethylpyrrocoline (Part VII, *J.*, 1955, 1504) (3 g.), methyl iodide (3 ml.), and methanol (8 ml.) were heated at 110—120° for 7 hr., then evaporated *in vacuo*. Trituration of the sticky residue with dry acetone gave a cream-coloured powder (1·3 g., 24%), m. p. 197°, which crystallised from ethanol in needles, m. p. 199—200°, identical with 1-ethyl-1 : 2 : 3-trimethylpyrrocolinium iodide from the previous experiment. The dark green acetone filtrate was diluted with dry ether (35 ml.) to precipitate an oil which crystallised when rubbed. The pale green solid (2·65 g., 48%) was collected and washed with acetone–ether, m. p. 158—166°. Crystallisation from acetone–ether gave straw-coloured crystals of *1-ethyl-2 : 3 : 3-trimethylpyrrocolinium iodide*, m. p. 179° (Found: C, 49·5; H, 5·6; N, 4·4%).

Reaction of 3-Ethyl-2-methylpyrrocoline with Methyl Iodide.—3-Ethyl-2-methylpyrrocoline (Part VIII, *loc. cit.*) (5 g.), methyl iodide (5 ml.), and methanol (12 ml.) were heated at 120° for 7 hr., then evaporated *in vacuo*. The green gum crystallised when rubbed with dry acetone, and addition of dry ether to the filtrate gave more solid. The combined crops (2·95 g.;

m. p. 157—162°) crystallised from acetone–ether in cream-coloured tablets of **3-*ethyl*-1 : 2 : 3-*trimethylpyrrocolinium iodide***, m. p. 167—168° (Found: C, 49·2; H, 5·8; N, 4·7; I, 40·0. $C_{12}H_{16}NI$ requires C, 49·5; H, 5·8; N, 4·4; I, 40·3%). As in most of the other alkylations, low-melting material could be recovered from the mother-liquors but could not be purified.

Reaction of Dimethylpyrrocolines with Cold Methyl Iodide.—2 : 5-Dimethylpyrrocoline (2·7 g.) in ether (15 ml.) was kept with methyl iodide (4 ml.) for 1 week, during which an oil slowly separated. The oil solidified when rubbed with acetone, and the resulting powder (0·65 g.) was crystallised from ethanol, to give pale green platelets of **2 : 5-*dimethylpyrrocoline hydriodide***, m. p. 188° (decomp.) (Found: C, 43·9; H, 4·7; N, 5·1; I, 46·0. $C_{10}H_{12}NI$ requires C, 44·0; H, 4·4; N, 5·1; I, 46·5%).

Similarly 2 : 7-dimethylpyrrocoline and methyl iodide gave **2 : 7-*dimethylpyrrocoline hydriodide***, green needles (from ethanol), m. p. 171—172° (Found: C, 44·2; H, 4·8; N, 5·0%). **1 : 2-*Dimethylpyrrocoline hydriodide***, similarly prepared, crystallised from ethanol–ether in pale blue-green needles, m. p. 177—179° (Found: C, 44·2; H, 4·8; N, 4·8%). All these hydriodides gave blue or violet dyes when treated with *p*-dimethylaminobenzaldehyde in alcohol. They also regenerated the parent pyrrocolines when treated with cold sodium hydroxide solution.

3(or 1)-p-***Dimethylaminobenzylidene-2-methylpyrrocolinium Iodide***.—A solution of 2-methylpyrrocoline (2·62 g.) and *p*-dimethylaminobenzaldehyde (2·98 g.) in ethanol (60 ml.) was treated with 55% hydriodic acid (2·8 ml.) and after 15 min. the deep blue *dye* (8·4 g.) was collected, washed with ethanol, and dried at 100°/4 mm. (Found: C, 55·4; H, 5·2; N, 7·3. $C_{18}H_{19}N_2I$ requires C, 55·4; H, 4·9; N, 7·2%). The product (no definite m. p.) was soluble in hot nitromethane but could not be recrystallised; it was only very sparingly soluble in most other solvents.

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Medicinal Chemistry Division, Beecham Research Laboratories Ltd.,
Betchworth, Surrey.
C. L. Bencard Ltd., Minerva Road,
Park Royal, London, N.W.10.

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The Configuration of Heterocyclic Antimony Compounds. Part III. Resolution and Racemisation of New Members of the 9-Stibiafluorene Series.*

By I. G. M. Campbell and D. J. Morrill.

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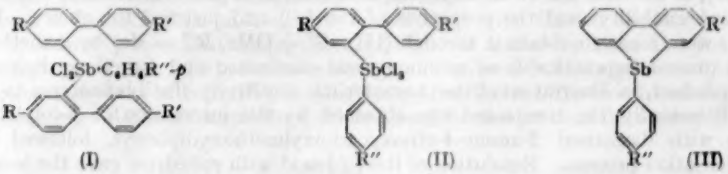
The synthesis and resolution of three new 9-stibiafluorenes is described. The specific rotation of these compounds varies considerably with the substituent present in the 2-position. Racemisation of 2-carboxymethoxy-9-*p*-tolyl-9-stibiafluorene observed in pyridine at four temperatures leads to an energy of activation of 14·4 kcal./mole, a value almost identical with that obtained for the corresponding 2-amino-compound in benzene. Unfortunately, it has not proved possible to prevent adventitious catalysis of the racemisation, a phenomenon shown by the amine and by both of the new acids examined. The cause of the dissymmetry of the stibiafluorenes is discussed, and further evidence in favour of a planar rather than a skew configuration of the tricyclic system is presented.

Earlier papers in this series * described the synthesis and optical resolution of 2-carboxy- and 2-amino-9-*p*-tolyl-9-stibiafluorene and recorded unsuccessful attempts to obtain enantiomers of 9-*p*-carboxyphenyl-9-stibiafluorene (III; R′ = H, R″ = CO_2H) in which the tricyclic portion of the molecule is unsubstituted. The two compounds previously resolved have the salt-forming group at position 2 and have specific rotations of the same

* Parts I and II, *J.*, 1950, 3109; 1952, 4448.

order. It was considered desirable to study how changes in the position of polar substituents affected rotatory power and optical stability, and to synthesise an active stibiafluorene sufficiently soluble for convenient investigation of its racemisation rate, but not subject to the adventitious catalysis observed in the earlier work.



The first compound chosen was 9-*p*-carboxyphenyl-2-methyl-9-stibiafluorene (III; R′ = Me, R″ = CO_2H), an isomer of the compound (III; R′ = CO_2H, R″ = Me) in which this type of dissymmetry was first demonstrated. The acid was synthesised through the intermediate (II) by the method described in Part I (*J.*, 1950, 3109), and the (−)-1-phenylethylamine salt gave immediate evidence of resolution. The isolation of the optically pure enantiomers, however, proved difficult because the solubilities of the diastereoisomeric salts were too close for ready separation, and free acid frequently separated from the salts despite the presence of excess of free (−)-amine in the solvents used for recrystallisation. Ephedrine was more effective as a resolving agent and the (+)-acid (−)-ephedrine salt, $[\alpha]_D$ +48·5°, was readily obtained, but second-order asymmetric transformation prevented the isolation of the more soluble salt in an optically pure condition. In one resolution fractions representing 85% of the salt separated with $[\alpha]_D$ +20° to +28°, giving acid with $[\alpha]_D$ +40° to +50°, and decomposition of the residual 15% of salt gave inactive acid. The specific rotation of the (+)-acid, $[\alpha]_D$ +78·0°, is low compared with that of the positional isomer (III; R′ = CO_2H, R″ = Me), which has $[\alpha]_D$ +245°. Evidently the rotatory contribution of the tricyclic residue is considerably reduced when the carboxyl group is replaced by methyl.

In the second compound examined (III; R′ = OMe, R″ = CO_2H), the *p*-carboxy-group was retained but methyl was replaced by the more polar methoxy-group. 2-Amino-4′-methoxydiphenyl required for the synthesis of this compound was obtained by nitration of 4-diphenylyl benzoate (cf. Jones and Chapman, *J.*, 1952, 1829) followed by hydrolysis, methylation, and reduction. In the course of the nitration a new mononitrophenol was obtained and shown to be 4-hydroxy-2-nitrodiphenyl (Campbell and Morrill, *Chem. and Ind.*, 1953, 1229). The position of the nitro-group in the compound follows from its oxidation to benzoic acid and its conversion, through the same series of reactions, into the same stibiafluorene (III; R′ = OMe, R″ = CO_2H) as was obtained from 4′-methoxy-2-nitrodiphenyl. For this acid also, ephedrine proved the most effective resolving agent, and, in contrast to all the other acids examined, the salts were optically stable in solution. (+)-1-Phenylethylamine used in the first attempts to resolve the acid gave successive fractions of salt with $[\alpha]_D$ +20·5°, +9·5°, and −85·9°, but crystallisation of the first of these from ethanol, ethyl acetate, or *n*-butanol failed to raise the specific rotation. Repeated crystallisation from chloroform, however, gave a salt, $[\alpha]_D$ +80·2°, obviously still optically impure and, from analysis, probably contaminated with free acid. The specific rotation of the more soluble fraction rose to $[\alpha]_D$ −103·4° on crystallisation, and (−)-acid obtained from it had $[\alpha]_D$ −145·5° ±2°. That this had not reached optical purity was proved by resolution with ephedrine, which gave a (+)-acid (−)-ephedrine salt, $[\alpha]_D$ +93·5°, yielding (+)-acid, $[\alpha]_D$ +153·0° ±1°. This value is effectively double that of (III; R′ = Me, R″ = CO_2H), and again illustrates the striking effect of the polar methoxy-group on the rotatory power of stibiafluorenes. Though the solubility of this acid in chloroform and in benzene was greater than that of (III; R′ = Me, R″ = CO_2H) it was still too low for a convenient study of racemisation in these solvents. A preliminary examination of the (−)-acid in pyridine indicated a half-life of 41·3 hours at 22° and 26·3 hours at 38°, when calculated from the initial rate constants, but, after racemisation had

proceeded to the extent of 20—25%, the rate became progressively slower, and, as insufficient active acid was available for a detailed study, no further work on it was done.

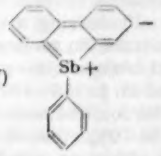
The search for a compound more suitable for determination of racemisation rates led to the study of 2-carboxymethoxy-9-*p*-tolyl-9-stibiafluorene (III; R′ = O·CH_2·CO_2H, R″ = Me), as introduction of the oxyacetic acid residue in place of carboxyl was expected to increase solubility, and the properties of the (±)-acid justified the choice. Initially attempts were made to obtain it through (III; R′ = OMe, R″ = Me) by demethylation, but this proved impracticable as antimony was eliminated and 4-methoxydiphenyl was the sole product, an illustration of the characteristic sensitivity of stibiafluorenes to halogen acids. Eventually the compound was obtained by the interaction of *p*-tolylstibonous chloride with diazotised 2-amino-4-ethoxycarbonylmethoxydiphenyl, followed by the usual cyclisation process. Resolution of the (±)-acid with ephedrine gave the less soluble (−)-acid (−)-ephedrine salt, $[\alpha]_D$ −147·5°, and the more soluble (+)-acid (−)-ephedrine salt, $[\alpha]_D$ +110·1°, and from these the active acids, $[\alpha]_D$ ±112·0° (*c* 0·3 in pyridine), were obtained. Isolation of the more soluble salt required considerable care as recrystallisation from boiling alcohol caused asymmetric transformation.

The specific rotation of this acid was considerably influenced by concentration, a characteristic not observed in any of the other stibiafluorenes. For example, values of $[\alpha]_D$ ranging from −112° to −145° were obtained when the acid was examined in pyridine at concentrations varying from 0·3 to 0·9 g. per 100 ml. Racemisation of the (−)-acid was initially followed in chloroform solution but consistent results could not be obtained despite rigorous precautions. For instance, a specimen of acid, $[\alpha]_D$ −112·0°, when examined in "AnalaR" chloroform not specially purified, had $[\alpha]_D$ −20·6° when first examined, and this fell to zero in 70 minutes. In carefully purified chloroform at 46·5°, two different specimens of optically pure acid gave racemisation rates of 1·7 and 1·8 × 10^{-3} min.$^{-1}$, and the rotation of (−)-acid in chloroform–acetic acid (1 : 1) at 26°, which had undergone only 15% racemisation in 29 hours, fell to zero in 55 minutes after the introduction of a trace of hydrochloric acid. The rate of this catalysed racemisation was 1·41 × 10^{-1} min.$^{-1}$ (half-life 5 minutes). Consistent results were obtained when the racemisation of portions of the same batch of acid was observed in pure pyridine at the same concentration, although a significant drop in rate occurred towards the end of the racemisation. Under these conditions the rate constants observed at 30°, 38°, 44°, and 46° were 3·8, 6·5, 10·4, and 12·7 × 10^{-4} min.$^{-1}$ respectively, and the resulting Arrhenius plot led to an energy of activation of 14·4 ± 0·5 kcal./mole, slightly lower than the value of 14·8 ± 0·5 obtained for the (+)-amine (III; R′ = NH_2, R″ = Me) when racemisation rates were measured in benzene (Part II, *loc. cit.*).

Weston (*J. Amer. Chem. Soc.*, **1954**, **76**, 2645) has concluded, from calculations based on a potential-energy function derived from known vibrational frequencies and molecular dimensions, that optically active derivatives of tervalent antimony should be stable at room temperature. In assessing the stability of the pyramidal molecule to inversion, Weston calculated the half-life of "racemisation" of trimethylstibine to be two hours at 67°, and, despite the vast structural difference between trimethylstibine and the stibiafluorenes, we considered that comparison of the calculated with an experimentally determined value would be of interest. Using the slope of the Arrhenius plot, in each case, we found that the half-life of the (−)-oxyacetic acid (III; R′ = O·CH_2·CO_2H, R″ = Me) was 115 minutes at 67°, and that of the (+)-amine (III; R′ = NH_2, R″ = Me) was 116 minutes. This remarkable agreement must, unfortunately, be regarded as fortuitous because, on investigating the (−)-acid (III; R′ = CO_2H, R″ = Me) (Part I, *loc. cit.*) we found that the half-life, determined in pyridine at 70°, was 89 hours, and it seems improbable that introduction of CO_2H in place of O·CH_2·CO_2H should exert such a pronounced stabilising effect if the inversion of the pyramidal molecule were the sole mechanism of racemisation. Further, Weston calculated the maximum energy of activation for the "racemisation" to be 26·7 kcal./mole, whereas our value is only 15 kcal./mole, and the difficulty we have experienced in obtaining reproducible results with all the active stibiafluorenes examined indicates that adventitious catalysis cannot be excluded with certainty.

As yet, no firm answer can be given to the question whether the dissymmetry of the

stibiafluorenes results from the stable pyramidal arrangement of the bonds round antimony or from a skew configuration of the benzene rings in the diphenyl system. But additional evidence, indicating that the whole tricyclic system is planar, has been obtained by comparison of the ultraviolet spectra of triphenylstibine and 9-*p*-tolyl-9-stibiafluorene (Campbell and Poller, *Chem. and Ind.*, 1953, 1126). The main absorption band of the stibiafluorene shows a bathochromic shift of 320 Å compared with that of triphenylstibine, indicating considerably increased conjugation between the antimony atom and the condensed ring system. If this interpretation is correct, the molecule is best represented by the numerous canonical forms of type (IV), in which every bond in the five-membered ring will have some double-bond character and the C–Sb bond will be shorter than the normal 2·11 Å.

(IV)  (V)

Scale drawings indicate that the five-membered ring can remain planar if α is 120°, β 107°, and θ 86° as in (V) (Part I, *loc. cit.*), but when the C–Sb bond length is shortened arbitrarily to 2·05 Å, the antimony bond angle becomes 89·6°, nearer the preferred value, and if α remains at 120°, β becomes 105°. Further, geometrical calculation shows that, if the benzene rings in the diphenyl system are rotated relative to one another, the total angular distortion in the five-membered ring will increase as shown in the Table 1. Obviously, the easing of

TABLE 1.

Angle between benzene rings	0°	10°	20°	30°
Total angular distortion	30°	33·4°	41·4°	51·3°
θ (Sb bond angle)	86°	86·4°	87·2°	88·6°

the strain at the antimony angle, θ, is small compared with the total strain in the other four angles of the five-membered ring, and it therefore seems unlikely that the stibiafluorene nucleus will show any serious deviation from the planar configuration. This conclusion is supported by the results of the recent *X*-ray crystal analysis of fluorene (Burns and Iball, *Nature*, 1954, **173**, 635) in which the maximum deviation from the plane is found to be 0·03 Å and the angles are α 107·6°, β 109·6°, and θ 105·6°.

A final decision on this problem should be possible through *X*-ray examination, and preliminary measurements on 9-*p*-ethoxycarbonylphenyl-9-stibiafluorene have been made by Mr. B. Chaudhuri, through the kindness of Dr. Lipson, Manchester. Crystal data so far available are included in the Experimental section and it is hoped that further work may give precise information on the shape of the stibiafluorene molecule.

EXPERIMENTAL

Substituted 2-Nitro- and 2-Amino-diphenyls.—4-Methyl-2-nitrodiphenyl was prepared by a modification of the method used by Ritchie (*J. Proc. Roy. Soc. New South Wales*, 1945, **78**, 169). 2-Nitro-*p*-toluidine (NH_2 = 1) (76 g.) was finely ground, stirred into a mixture of concentrated hydrochloric acid (180 ml.) and water (70 ml.), and diazotised with a saturated solution of sodium nitrite (35 g.). The diazonium salt solution was filtered and poured into ice-cold benzene (1100 ml.), followed by a solution of sodium acetate (180 g.) in water (350 ml.). The mixture was stirred vigorously for 3 hr. at 10° and then for 48 hr. at room temperature. The upper layer was separated, the benzene removed by distillation, and the residual oil extracted several times with light petroleum (b. p. 40—60°). The extracts were filtered through a short column of alumina, the dark impurities remaining as a slowly-moving band, while the required compound appeared in the filtrate. Removal of the solvent from this filtrate left a pale orange-yellow, viscous oil which rapidly crystallised. From light petroleum (b. p. 40—60°), containing a trace of methylene chloride, this separated as pale yellow crystals, m. p. 48·5—50° (Found: C, 73·3; H,

5·4; N, 6·4. Calc. for $C_{13}H_{11}O_2N$: C, 73·2; H, 5·2; N, 6·6%). This compound has previously been reported as an oil, b. p. 208°/11 mm. (Ritchie, *loc. cit.*). It was reduced by the method recommended in *Org. Synth.*, Vol. II, p. 448, for the reduction of 2-nitrofluorene. The amine was isolated as the hydrochloride (m. p. 194—200°), and gave an acetyl derivative, m. p. 147—148°, which corresponds to the reported value for 2-acetamido-4-methyldiphenyl (Ritchie, *loc. cit.*).

Nitration of 4-Diphenylyl Benzoate.—A mixture of acetic anhydride (60 ml.) and fuming nitric acid (30 ml.) was added slowly to a well-stirred suspension of 4-diphenylyl benzoate (55 g.) in acetic anhydride (400 ml.) at 20—30°. Stirring was continued for a further 4 hr. The mixture was then filtered and the solid (A), a mixture of 2′- and 4′-nitro-4-diphenylyl benzoates, washed with water and dried. When the filtrate was diluted cautiously with water (180 ml.) below 25°, a yellow crystalline solid (B) slowly separated.

Fraction (A) was extracted with hot acetone (400 ml.), leaving a residue of 4′-nitro-4-diphenylyl benzoate, m. p. 208—212° (20·5 g.), and the filtrate, on cooling and dilution with a little water, gave yellow crystals of 2′-nitro-4-diphenylyl benzoate, m. p. 145—155° (11·4 g.) (Jones and Chapman, *J.*, 1952, 1829, record m. p. 212° and m. p. 156—157° respectively).

The mixture (B) was not easily separable by crystallisation and accordingly the benzoates were hydrolysed by boiling potassium hydroxide (10% in 70% ethanol) (5 min.). The deep red solution was cooled and filtered from a solid residue consisting mainly of potassium salts of polynitro-compounds. The filtrate was just acidified with dilute hydrochloric acid and neutralised with excess of saturated sodium hydrogen carbonate solution. The oily phenols which separated were extracted with ether and the extracts washed once with saturated sodium hydrogen carbonate solution. The ether solution was then extracted twice with 16% sodium hydroxide solution. Addition of excess of acetic anhydride to the combined alkaline extracts caused almost instantaneous acetylation, and, from the mixture of acetates deposited, boiling ethanol (2 × 75 ml.) extracted 2′-nitro-4-diphenylyl acetate, m. p. 122—124° (6·8 g.) (Copp and Walls, *J.*, 1950, 311, record m. p. 122°). The insoluble residue on recrystallisation from acetone, or better, ethyl acetate, gave *2-nitro-4-diphenylyl acetate*, m. p. 169° (4·0 g.), as transparent chunky prisms (Found: C, 65·4; H, 4·1. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%).

Characterisation of 2-Nitro-4-diphenylyl Acetate.—The compound was hydrolysed by boiling 10% alcoholic potassium hydroxide (5 min.) and the *phenol* was recrystallised from 1 : 1 benzene–light petroleum (b. p. 60—80°); it had m. p. 141—143° (Found: C, 67·1; H, 4·4. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2%). It gave a *benzoate*, m. p. 105—106° (Found: C, 71·5; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 71·4; H, 4·2%), and a methyl ether, m. p. 72° (Found: C, 68·1; H, 5·0%. Calc. for $C_{13}H_{11}O_3N$: C, 68·1; H, 4·8%). Copp and Walls (*loc. cit.*) report 4-methoxy-2-nitrodiphenyl, m. p. 75—77°.

Oxidation of the phenol (1·5 g.) in sodium hydroxide with potassium permanganate gave benzoic acid (0·5 g.), m. p. and mixed m. p. 121—122°. This proves that the nitro- and the hydroxyl group are present in the same ring, and as the known, steam-volatile 4-hydroxy-3-nitrodiphenyl has m. p. 66°, the present compound, m. p. 141—143°, must be 4-hydroxy-2-nitrodiphenyl. This has been substantiated by conversion of both this compound and the isomeric 4-hydroxy-2′-nitrodiphenyl into the same heterocyclic antimony compound, 9-*p*-ethoxycarbonylphenyl-2-methoxy-9-stibiafluorene (see p. 1667 and Table 2).

Attempted Reduction of 2′-Nitro-4-diphenylyl Benzoate.—The reduction of this compound with iron and acetic acid, stannous chloride and hydrochloric acid, or palladised charcoal and *cyclo*hexene was unsuccessful; only unchanged starting material or brightly coloured decomposition products were isolated. Reduction in dilute acetic acid or in ethanol with zinc dust gave a poor yield of a *compound*, m. p. 127°, which analysed correctly for the required amine (Found: C, 79·0; H, 5·5. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%), but which could not be diazotised under normal conditions and did not form a stannichloride or a satisfactory acetyl derivative.

2′-Amino-4-methoxydiphenyl—2′-Nitro-4-diphenylyl benzoate was hydrolysed by boiling 10% alcoholic potassium hydroxide (5 min.), and the phenol, m. p. 113—116°, was methylated in sodium hydroxide with methyl sulphate giving 4-methoxy-2′-nitrodiphenyl, m. p. 58—62° (Jones and Chapman, *loc. cit.*, recorded m. p. 64°; Copp and Walls, *loc. cit.*, gave m. p. 60—60·5°). Reduction by zinc dust in neutral solution (*Org. Synth.*, Vol. II, p. 448) gave 2-amino-4′-methoxydiphenyl, characterised as the benzoyl derivative, m. p. 84—85°, a value considerably lower than that recorded by Copp and Walls (*loc. cit.*) who found m. p. 108° (Found: C, 79·2; H, 5·8. Calc. for $C_{20}H_{17}O_2N$: C, 79·2; H, 5·7%), and the *p*-nitrobenzoate, m. p. 163—164° (Copp and Walls, *loc. cit.*, give m. p. 164—165°).

2-Amino-4-methoxydiphenyl.—This was prepared from the corresponding nitro-compound by a similar reduction, isolated as the hydrochloride, and characterised as the *p*-nitrobenzoate, m. p. 168—169°, and the *benzoyl derivative*, m. p. 144—145° (Found: C, 78·8; H, 5·7. $C_{20}H_{17}O_3N$ requires C, 79·2; H, 5·7%).

2'-Nitro-4-diphenylyloxyacetic Acid.—4-Hydrozy-2'-nitrodiphenyl (18·2 g.) was dissolved in a solution of sodium hydroxide (12 g.) in water (35 ml.). To this solution was added monochloroacetic acid (16 g.) and sodium hydroxide (6·9 g.) in water (18 ml.), and the whole heated for 2 hr. on a boiling-water bath. A further portion of monochloroacetic acid (16 g.) was then added followed by sodium hydroxide solution (16%) until the red colour of the phenoxide ion was restored, and heating was continued for a further hour. The product consisted of unchanged phenol (4 g.) and crude 2'-nitro-4-diphenylyloxyacetic acid, m. p. 147—156° (17·3 g.). Two recrystallisations from ethyl acetate–light petroleum (b. p. 60—80°) (2 : 1) gave the pure *acid*, m. p. 160—161° (13 g.) (Found: C, 61·6; H, 4·1%; equiv., 273·5. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·1%; equiv., 273·2).

Ethyl 2'-Amino-4-diphenylyloxyacetate.—Esterification of 2'-nitro-4-diphenylyloxyacetic acid (55 g.) in absolute ethanol (500 ml.) containing dry hydrogen chloride gave a viscous yellow oil (56 g.), b. p. 180—185°/8 × 10^{-4} mm., which failed to crystallise. This was reduced in neutral solution with zinc dust, and the crude *amino-ester* (37·6 g.) was distilled, having b. p. 172—180°/8 × 10^{-3} mm., m. p. 55—56° (Found: C, 70·5; H, 6·4. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3%). The aqueous mother-liquor from the reduction, on cooling to 0°, deposited the amino-acid (9 g.), which was esterified with absolute ethanol and dry hydrogen chloride, giving the amino-ester hydrochloride, m. p. 180—186° (8 g.).

Preparation of Diarylstibinic Chlorides (II).—Compounds of this type were obtained in 20—35% yield by the reaction described in Part I (*J.*, 1950, 3109). The diazonium antimony chloride double salt obtained from the required amine was decomposed in the presence of a molecular proportion of either *p*-ethoxycarbonylphenyl- or *p*-tolyl-stibonous chloride in ethanol by addition of a catalytic quantity of copper bronze. Any triarylstibine dichloride (I) formed usually crystallised from the mixture at this stage and was removed, and the diarylstibinic chloride (II) was isolated from the filtrate by precipitation with hydrochloric acid or by crystallisation, after evaporation (vacuum) of most of the ethanol. In this way, the double salt prepared from 2-amino-4-methyldiphenyl hydrochloride (8 g.) gave p-*ethoxycarbonylphenyldi-(4-methyl-2-diphenylyl)stibine dichloride* (I; R = Me, R' = H, R'' = CO_2Et), m. p. 252° (2 g.) (Found: C, 62·4; H, 4·9. $C_{33}H_{31}O_2Cl_2Sb$ requires C, 62·2; H, 4·6%), and p-*ethoxycarbonylphenyl-4-methyl-2-diphenylylstibinic chloride* (II; R = Me, R' = H, R'' = CO_2Et), m. p. 164—166° (4 g.) (Found: C, 48·0; H, 3·7. $C_{23}H_{20}O_2Cl_2Sb$ requires C, 48·5; H, 3·7%). Both compounds were recrystallised from carbon tetrachloride. Reduction of (II) with stannous chloride in ethanol gave the corresponding *stibinous chloride*, m. p. 121—122° (Found: C, 55·5; H, 4·3. $C_{22}H_{20}O_2ClSb$ requires C, 55·8; H, 4·3%). When 2-amino-4'-methoxydiphenyl hydrochloride (15 g.) was coupled with *p*-tolylstibonous chloride, a negligible quantity of insoluble dichloride separated and was not characterised. Evaporation of the filtrate gave *4'-methoxy-2-diphenylyl-p-tolylstibinic chloride* (II; R = H, R' = OMe, R'' = Me), m. p. 153—154° (5·1 g.) (Found: C, 47·6; H, 3·5. $C_{20}H_{18}OCl_2Sb$ requires C, 47·8; H, 3·6%). The same amine hydrochloride (10·9 g.) with *p*-ethoxycarbonylphenylstibonous chloride gave p-*ethoxycarbonylphenyldi-(4'-methoxy-2-diphenylyl)stibine dichloride* (I; R = H, R' = OMe, R'' = CO_2Et), m. p. 247—248° (1 g.) (Found: C, 58·8; H, 4·6. $C_{35}H_{31}O_4Cl_2Sb$ requires C, 59·4; H, 4·4%), and p-*ethoxycarbonylphenyl-4'-methoxy-2-diphenylylstibinic chloride*, m. p. 169—170° (II; R = H, R' = OMe, R'' = CO_2Et) (5·2 g.) (Found: C, 46·5; H, 3·5. $C_{23}H_{20}O_3Cl_2Sb$ requires C, 47·1; H, 3·6%). Similarly, the isomeric 2-amino-4-methoxydiphenyl hydrochloride (12 g.) gave only traces of dichloride and p-*ethoxycarbonylphenyl-4-methoxy-2-diphenylylstibinic chloride* (II; R = OMe, R' = H, R'' = CO_2Et), m. p. 139—141° (5·5 g.), after crystallisation from light petroleum (b. p. 100—120°) (Found: C, 47·6; H, 3·6%). Ethyl 2'-amino-4-diphenylyloxyacetate (27 g.) reacted with *p*-tolylstibonous chloride to give the insoluble *di-4'-carboxymethoxy-2-diphenylyl-p-tolylstibine dichloride* (I; R = H, R' = $O{\cdot}CH_2{\cdot}CO_2Et$, R'' = Me), m. p. 196—197° (3·5 g.) (Found: C, 58·5; H, 4·9. $C_{39}H_{37}O_6Cl_2Sb$ requires C, 59·0; H, 4·7%), and addition of hydrochloric acid to the filtrate precipitated *4'-ethoxycarbonylmethoxy-2-diphenylyl-p-tolylstibinic chloride* (II; R = H, R' = $O{\cdot}CH_2{\cdot}CO_2Et$, R'' = Me), m. p. 131—132° (10 g.), after recrystallisation from benzene–light petroleum (b. p. 60—80°) (1 : 2) (Found: C, 48·5; H, 4·2. $C_{25}H_{22}O_3Cl_2Sb$ requires C, 48·1; H, 3·9%). On evaporation of the mother-liquor at room temperature (vacuum) a further fraction of crystalline material (5 g.) separated. On crystallisation from benzene–light petroleum (b. p. 60—80°),

this gave *4'-ethoxycarbonylmethoxy-2-diphenylylstibonous chloride*, m. p. 142—143° (Found: C, 43·6; H, 3·7; Sb, 27·0. $C_{16}H_{15}O_3Cl_2Sb$ requires C, 42·9; H, 3·4; Sb, 27·2%).

Preparation of 9-Stibiafluorenes (III).—The diarylstibinic chlorides were converted into the corresponding acids by addition, in acetone solution, to aqueous sodium acetate. The precipitated acids, after thorough drying at room temperature (vacuum) were cyclised by dehydration in acetic anhydride containing sulphuric acid, and the crude 9-stibiafluorene oxides were isolated by dilution with a large volume of water. The oxides were not characterised but were reduced, while still moist, with stannous chloride in acetone (*J.*, 1952, 4448). The pure 9-stibiafluorenes were obtained in 50—65% yield, usually after one crystallisation. The properties of the *compounds* are listed in Table 2.

TABLE 2. *9-Stibiafluorenes* (III).

				Found (%)				Required (%)		
R'	R''	M. p.	Solvent	C	H	Sb	Formula	C	H	Sb
Me	CO_2Et	155—156°	EtOAc–EtOH	60·0	4·4	—	$C_{22}H_{19}O_2Sb$	60·4	4·4	27·9
Me	CO_2H	240	AcOH	58·4	3·7	29·6	$C_{20}H_{15}O_2Sb$	58·7	3·7	29·8
OMe	Me	117—118	MeOH	60·6	4·3	30·9	$C_{20}H_{17}OSb$	60·8	4·3	30·8
OMe	CO_2Et	147—148	EtOAc–EtOH	58·0	4·5	—	$C_{23}H_{19}O_3Sb$	58·3	4·2	26·9
OMe	CO_2H	231	AcOH	57·0	3·6	28·6	$C_{21}H_{15}O_3Sb$	56·5	3·6	28·6
$O{\cdot}CH_2{\cdot}CO_2Et$	Me	132—133	EtOH	59·8	4·1	—	$C_{23}H_{21}O_3Sb$	59·1	4·5	26·1
$O{\cdot}CH_2{\cdot}CO_2H$	Me	164—165	AcOH	57·1	3·9	27·8	$C_{21}H_{17}O_3Sb$	57·4	3·9	27·7

The free acids were obtained from the corresponding esters by hydrolysis with 5% alcoholic potassium hydroxide. An attempt to demethylate (III; R' = OMe; R'' = Me) by hydrobromic acid in acetic acid or by aluminium chloride in benzene resulted in extensive decomposition, and the only product isolated from either experiment was 4-methoxydiphenyl, m. p. and mixed m. p. 88—89°.

Resolutions of 9-p-Carboxyphenyl-2-methyl-9-stibiafluorene.—Rotations were measured at room temperature in "AnalaR" chloroform (*c* 0·2—0·5) in 2-dm. tubes, unless otherwise stated.

Preliminary experiments showed that the acid formed salts with cinchonine, quinine, ephedrine, and (−)-1-phenylethylamine. The cinchonine salt was separated into three fractions varying in specific rotation from $[\alpha]_D$ + 63·5° to 69·8°, but acid regained from them was optically inactive. The *quinine salt*, m. p. 205—206°, $[\alpha]_D$ − 67·4° (Found: C, 65·1; H, 5·6. $C_{39}H_{15}O_3Sb,C_{20}H_{24}O_2N_2$ requires C, 65·5; H, 5·4%), proved equally ineffective as a resolving agent, and the quinidine salt separated as a syrup and did not crystallise. Results obtained with (−)-1-phenylethylamine were initially encouraging for, when the acid (5 g., 0·012 mole) and (−)-amine (3 g., 0·025 mole) were dissolved together in ethyl acetate (900 ml.) the first crop of crystals (5·36 g.) had $[\alpha]_D$ −6·7° and the second crop (0·76 g.) had $[\alpha]_D$ +15·8°. However, even after eight recrystallisations of the first fraction from chloroform–ethanol (1 : 2), the *salt* obtained (0·1 g.; $[\alpha]_D$ −79·3°) was not optically pure (Found: C, 63·4; H, 4·9. $C_{39}H_{15}O_3Sb,C_8H_{11}N$ requires C, 63·4; H, 4·9%). Recrystallisation of the second crop, $[\alpha]_D$ +15·8°, gave two fractions, comprising all the material, but these had $[\alpha]_D$ −7·9° and −16·1°, indicating that second-order asymmetric transformation had occurred. A second attempt using (+)-1-phenylethylamine was even less satisfactory, the most dextrorotatory salt obtained having $[\alpha]_D$ +59·2°. It was essential to recrystallise the salts from solvent containing free amine, otherwise the solid which separated was contaminated with free acid. The m. p.s of all fractions were indeterminate, ranging from 200° to 215°.

Resolution with ephedrine. The acid (8·2 g., 0·02 mole) was suspended in boiling ethanol (150 ml.), and ephedrine hydrate (4·0 g., 0·022 mole) added. Addition of chloroform (20 ml.) gave an almost clear solution, which was filtered and set aside overnight. The first fraction of salt (5·5 g.) had $[\alpha]_D$ +7·5°, and three recrystallisations of this from the minimum volume of ethanol gave the pure *(+)-acid (−)-base salt*, m. p. 200—201°, $[\alpha]_D$ +48·5° (1·8 g.), as flat needles (Found: C, 62·3; H, 5·3. $C_{39}H_{15}O_3Sb,C_{10}H_{15}ON$ requires C, 62·7; H, 5·3%). The second fraction of salt (1·25 g.) obtained by evaporation (vacuum) of the mother-liquor to 80 ml. had $[\alpha]_D$ −34·4°, but contained free acid, and recrystallisation of this, and also of the third fraction (1·75 g.), $[\alpha]_D$ −6·1°, failed to give the optically pure (−)-acid (−)-base salt. The most lævorotatory fraction obtained had $[\alpha]_D$ −52·3°.

In a second resolution ephedrine (4·5 g., 0·025 mole) was added to the acid (8·2 g., 0·02 mole) in ethanol (200 ml.) and chloroform (20 ml.). The first fraction was separated after 24 hr., and later fractions were obtained by evaporating the filtrate (vacuum) at room temperature

until crystallisation started and then warming it to effect solution again. This procedure separated the salt into fractions: 4·5 g., $[\alpha]_D$ +28·3°; 1·45 g., $[\alpha]_D$ +21·5°; 1·05 g., $[\alpha]_D$ +19·7°; 1·55 g., $[\alpha]_D$ +27·2°; and 1·8 g., $[\alpha]_D$ +25·2°. From the residual mother-liquor acid regained (0·92 g.) was optically inactive. Three recrystallisations of the first fractions gave pure (+)-acid (−)-base salt (1·9 g.), m. p. 200—201°, $[\alpha]_D$ +48·6°, and a further 1·1 g. were obtained from later fractions. Again all attempts to obtain the (−)-acid (−)-base salt in optically pure condition failed, but one small fraction isolated had $[\alpha]_D$ −64·7° (Found: C, 62·4; H, 5·7%).

Resolution of 9-p-*Carboxyphenyl*-2-*methoxy*-9-*stibiafluorene*.—The acid formed crystalline salts with (+)-1-phenylethylamine and with ephedrine and the solubility relations of the former appeared suitable for resolution. Accordingly the acid (5 g., 0·012 mole) and the (+)-amine (1·86 g., 0·024 mole) were dissolved together in boiling ethanol (500 ml.), and a first crop of *salt*, X1, m. p. 195—196°, $[\alpha]_D$ +20·5° (1·8 g.), was collected after 2 hr. (Found: C, 61·1; H, 4·9. $C_{29}H_{15}O_3Sb,C_8H_{11}N$ requires C, 61·6; H, 4·8%). A second crop, X2, $[\alpha]_D$ +9·4° (2·7 g.), was obtained when the filtrate was kept overnight; and X3, $[\alpha]_D$ −85·9° (0·5 g.), was isolated after evaporation to 50 ml. Initially X1 appeared to be optically pure, as recrystallisation from ethanol or ethyl acetate or *n*-butanol failed to raise the specific rotation. However, on crystallisation from chloroform containing a little (+)-amine, the $[\alpha]_D$ increased slowly. X2 on crystallisation from ethanol gave a further fraction of salt, $[\alpha]_D$ +20·4°, and this was combined with X1 and recrystallised eight times from chloroform to give a salt, $[\alpha]_D$ +80·5° (0·17 g.). Obviously this was still optically impure by comparison with X3. Two recrystallisations of X3 from ethanol gave 0·12 g. of salt, m. p. 199—201°, $[\alpha]_D$ −103·4° ±3° (Found: C, 61·6; H, 5·2%), but this had not reached optical purity. The unsatisfactory results of this resolution were caused partly by dissociation of the salt and separation of free acid, and partly by second-order asymmetric transformation. Evidence for this was obtained when a fraction of salt with zero rotation was crystallised from chloroform and recovered quantitatively with $[\alpha]_D$ +18·9°.

Resolution with ephedrine. The acid (0·8 g.) was added to a solution of ephedrine hydrate (0·4 g., 1·2 equivs.) in boiling ethanol (50 ml.). After 48 hr., the first fraction of salt, $[\alpha]_D$ +14·9° (0·7 g.), was collected. Three recrystallisations of this from absolute ethanol containing 0·2% of ephedrine gave pure (+)-acid (−)-base salt, as small plates, m. p. 193—196°, $[\alpha]_D$ +93·5° ±1·2°, unchanged by further crystallisations (Found: C, 60·5; H, 5·3. $C_{29}H_{15}O_3Sb,C_{10}H_{15}ON$ requires C, 61·0; H, 5·1%). The second fraction of salt, which separated after concentration, had $[\alpha]_D$ −40°, and two recrystallisations of this gave 0·1 g. of salt, m. p. 188—191°, $[\alpha]_D$ −94·7°. Unfortunately lack of material prevented the isolation of the pure (−)-acid (−)-base salt. This should be possible as the ephedrine salts were optically stable in solution and no evidence of asymmetric transformation was observed.

Resolution of 9-*Tolyl*-9-*stibiafluorenyl*-2-*oxyacetic Acid*.—A solution of the acid (6·2 g.) and ephedrine hydrate (3·1 g., 1·2 equivs.) in boiling ethanol (50 ml.) cooled for 5 hr. deposited crop A1 (2·55 g.), $[\alpha]_D$ −128·5°, crop A2 (3·8 g.), $[\alpha]_D$ +42·4°, after a further 5 hr., and crop A3 (0·65 g.), $[\alpha]_D$ +91·0°, after concentration to 5 ml. The presence of excess of ephedrine in the mother-liquor prevented the crystallisation of the residual salt. Two recrystallisations of A1 from ethanol gave (−)-*acid* (−)-*base salt*, m. p. 184°, $[\alpha]_D$ −147° ±1·5° (1·5 g.) unchanged by further crystallisation (Found: C, 61·9; H, 5·5; Sb, 20·1. $C_{31}H_{17}O_3Sb,C_{10}H_{15}ON$ requires C, 61·6; H, 5·3; Sb, 20·1%). A second fraction from the second crystallisation had $[\alpha]_D$ −146·0°. Recrystallisation of A2 provided a further fraction of salt with $[\alpha]_D$ −147·1°, and second-order asymmetric transformation was demonstrated when a salt, $[\alpha]_D$ −3·3° (1·2 g.), was recrystallised and recovered in two fractions, $[\alpha]_D$ −147·0° ±2° (0·7 g.), and $[\alpha]_D$ −90·3° (0·4 g.). However, two recrystallisations of A3 gave (+)-acid (−)-base salt, m. p. 173°, $[\alpha]_D$ +110·1° ±2·0° (0·12 g.), which must have been substantially optically pure, though analysis indicated that it contained free acid (Found: C, 60·0; H, 5·4%). ($[\alpha]_D$ were measured in absolute ethanol, *c* 0·2 approx.)

Isolation of the Optically Active Acids.—Decomposition of an alcoholic solution of the salts with 0·1N-sulphuric acid at −20° proved the best method of isolating the active acids. Decomposition at room temperature or insufficient washing of the precipitated acid resulted in slight racemisation. Specific rotations were measured in pyridine (*c* 0·2—0·5), and the properties of the *acids* are listed in Table 3.

Racemisation of the Optically Active Acids.—The pyridine (May and Baker's pure) used for racemisation experiments was dried over potassium hydroxide and fractionally distilled. "AnalaR" chloroform was shaken with anhydrous sodium carbonate before use, a precaution which was found essential, for, when it was omitted, low values of $[\alpha]_D$ were obtained initially

and rapid racemisation occurred. The acids (0·05—0·2 g.) were dissolved in 20 ml. of solvent at the required temperature and racemisation was observed in a jacketed polarimeter tube (l = 2 dm.). Rate constants [$k = (\ln \alpha_0/\alpha_t)/t$ in min.$^{-1}$] were evaluated graphically, from the readings given in Table 4. In every case, the racemisation was followed for considerably longer

TABLE 3. *Optically active acids* (III).

R′	R″	Resolving agent	Salt, $[\alpha]_D$	Solvent	Acid $[\alpha]_D$ in pyridine	M. p.	Found (%) C	Found (%) H
Me	CO_2H	(−)-CHPhMe·NH_2	− 79·3°	$CHCl_3$	− 69·2°	225—238°	59·0	3·9
Me	CO_2H	Ephedrine	+ 48·5	$CHCl_3$	+ 78·0	224—232	58·6	3·9
OMe	CO_2H	(−)-CHPhMe·NH_2	−103·4	$CHCl_3$	−145·5	212—215	56·5	3·7
OMe	CO_2H	Ephedrine	+ 93·5	$CHCl_3$	+153·0	221—223	56·4	3·8
O·CH_2·CO_2H	Me	Ephedrine	−147·5	EtOH	−112·5	149—151	55·8	4·3 (+ H_2O)
O·CH_2·CO_2H	Me	Ephedrine	+110·1	EtOH	+112·0	149—151	55·6	4·2 (+ H_2O)

TABLE 4. *Rates of racemisation.*

Compound	Temp.	Wt. (g.) in 20 ml.	Initial α_D	Final α_D	Time (min.)	10^4k	Half-life (hours)
(III) R′ = OMe, R″ = CO_2H	22°	0·1094	+1·68°	+1·52°	340	2·8	41·3
	38	0·0625	+0·89	+0·76	360	4·4	26·3
(III) R′ = O·CH_2·CO_2H, R″ = Me	30	0·1814	−2·64	−2·03	725	3·8	30·4
	38	0·1818	−2·63	−1·80	643	6·5	17·8
	44	0·1431	−1·74	−1·11	386	10·4	11·1
	46	0·1755	−2·54	−1·41	481	12·7	9·1
	38	0·1042	+0·95	+0·64	418	9·5	12·2
(III) R′ = O·CH_2·CO_2H, R″ = Me	46·5	0·0713 *	−0·83	−0·49	320	16·7	6·9
	46·5	0·058 *	−0·50	−0·22	454	18·4	6·3
(III) R′ = CO_2H, R″ = Me	70	0·0500	−1·22	−0·94	1920	1·3	88·9

* In $CHCl_3$; other experiments in pyridine.

but the rate gradually decreased. In the last experiment tabulated, 0·2500 g. of the active acid was dissolved in 100 ml. of pyridine at 18·5°. Eight small flasks were filled with the solution, placed in a thermostat at 70°, and withdrawn at intervals, and cooled rapidly, and the readings were taken at 18·5°.

Crystal Data for 9-p-*Ethoxycarbonylphenyl*-9-*stibiafluorene*.—Triclinic; cell dimensions, a = 9·05, b = 15·68, c = 8·05 Å; α = 112·7°, β = 99·6°, γ = 113·97°. Two molecules per unit cell, space group $P\bar{1}$, d calc., 1·60 (found 1·62). The co-ordinates of the Sb atoms are x = 2·24, y = 1·70, z = 0·88 Å.

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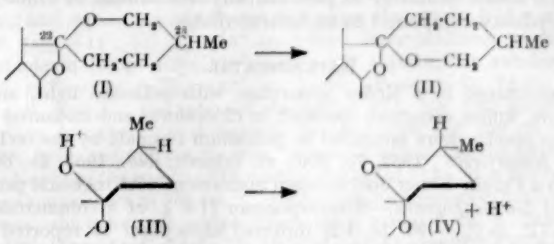
Epimerisation at $C_{(25)}$ *of Steroid Sapogenins: Sarsasapogenin, neoTigogenin, and Sisalagenin.*

By R. K. Callow and V. H. T. James.

[Reprint Order No. 6052.]

The transformation of three "normal" sapogenins, sarsasapogenin, *neo*-tigogenin, and sisalagenin, into the "*iso*-"isomerides, smilagenin, tigogenin, and hecogenin, respectively, has been examined, and the inversion of configuration at $C_{(25)}$ confirmed. Sisalagenin, the $C_{(25)}$-epimer of hecogenin, has been isolated from the sapogenins of *Agave sisalana*.

The work of Scheer, Kostic, and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 4871) appears to establish that sarsasapogenin and smilagenin differ in configuration at $C_{(25)}$ and hence to disprove Marker's hypothesis that "normal" and "*iso*-"sapogenins differ only in their steric arrangement at $C_{(22)}$ (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1949, 3rd edn.). This revision naturally provoked a re-examination of the reported conversion of sarsasapogenin into smilagenin (Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 846), of yamogenin into diosgenin, and of *neo*-tigogenin into tigogenin (Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *ibid.*, 1947, **69**, 2167). This reaction was previously explained by the opening and closing of an oxide ring at $C_{(22)}$ [(I) ⟶ (II)] but now requires, to explain it, a mechanism of inversion of configuration at $C_{(25)}$ such as that suggested by Cornforth [(III) ⟶ (IV)] (*Ann. Reports*, 1953, **50**, 219).



We were able to confirm the occurrence of this isomerisation, brought about by boiling a solution of the steroid in ethanol and concentrated hydrochloric acid for 120 hr., with sarsaspogenin and *neo*tigogenin and extended the investigation to a new "normal" sapogenin, sisalagenin. *neo*Tigogenin and sisalagenin have been obtained from the crystallisation residues of the acetate of hecogenin extracted from sisal, *Agave sisalana* Perrine (Callow, Cornforth, and Spensley, *Chem. and Ind.*, 1951, 699; Spensley, *ibid.*, 1952, 426), made available to us by the kindness of Messrs. T. and H. Smith of Edinburgh with the permission of the National Research Development Corporation.

Sisalagenin, which has not been described before, is a ketonic sapogenin, isomeric with hecogenin, which we find to be the "normal" analogue of the latter, epimeric with it at $C_{(25)}$. Sisalagenin acetate was separated * in small amount from the more soluble fractions of the ketonic part of the crystallisation residues, obtained by the use of Girard's reagent T. Sisalagenin,† obtained by hydrolysis, had an optical rotation slightly more negative than that of hecogenin $\Delta([M_D]_{S\text{-}H} = -48°)$: this is comparable with sarsasapogenin–smilagenin, $\Delta[M_D] = -42°$, and *neo*tigogenin–tigogenin, $\Delta[M_D] = -33°$. Its infrared absorption spectrum showed the bands typical of "normal" sapogenins, in particular one

* In the course of this investigation Professor F. S. Spring kindly informed us that he had isolated the "normal" isomer of hecogenin, but, in view of our work, he most courteously refrained from continuing his own investigation.

† In view of the confusion of prefixes in this group, the impossibility of legitimately maintaining the name "*neo*hecogenin" used for an imperfectly characterised compound by Marker and Lopez (*J. Amer. Chem. Soc.*, 1947, **69**, 2373), and the uncertainty attaching to certain details of configuration, it has been thought preferable to invent a new trivial name for this compound.

at 921 cm.$^{-1}$ some 4 times the height of one at 897 cm.$^{-1}$, and a band at 851 cm.$^{-1}$, but only a weak one at 863 cm.$^{-1}$. Converted into a *pseudo*sapogenin in the usual way it yielded, by opening of ring F, *pseudo*sisalagenin which, in a potassium bromide disc, has an infrared absorption practically indistinguishable from that of *pseudo*hecogenin. Oxidation of this with chromic acid yielded (+)-α-methylglutaric acid and *allo*pregn-16-ene-3 : 12 : 20-trione, proving that $C_{(25)}$ has the configuration opposite to that of $C_{(25)}$ of hecogenin which yields the same pregnene derivative and (−)-α-methylglutaric acid (cf. James, *J.*, 1955, 637).

Treatment of sisalagenin with boiling ethanolic hydrochloric acid yielded hecogenin, characterised by m. p., optical rotation, infrared absorption, and conversion into the acetate.

*neo*Tigogenin, first reported by Goodson and Noller (*J. Amer. Chem. Soc.*, 1939, **61**, 2420) as accompanying tigogenin from *Chlorogalum pomeridianum* Kunth, is also a companion of tigogenin in the non-ketonic fraction of sisal sapogenins and is separable by a rather tedious fractional crystallisation of the acetates. *pseudoneo*Tigogenin, prepared by the usual method, had an infrared absorption in potassium bromide practically indistinguishable from that of *pseudo*tigogenin. Oxidation with chromic acid yielded (+)-α-methylglutaric acid. Epimerisation of *neo*tigogenin by boiling ethanolic hydrochloric acid yielded tigogenin, characterised by its physical properties, and, to remove all possible doubt that inversion at $C_{(25)}$ actually occurs, the tigogenin obtained in this way was degraded to give the α-methylglutaric acid: this was lævorotatory. In this instance alternative conditions of epimerisation were investigated. Transformation of *neo*tigogenin into tigogenin took place in hot dioxan containing concentrated hydrochloric acid. Under similar conditions epimerisation occurred in the presence of acetic anhydride, a circumstance which seems definitely to preclude any mechanism in which an oxide ring is opened giving a hydroxy-compound as an intermediate.

Experimental

M. p.s were determined in a Kofler apparatus, with polarised light, and are corrected. Optical rotations are, unless otherwise specified, in chloroform and measured in a 4-dm. tube. Infrared absorption spectra were measured in potassium bromide by the technique of Schiedt and Reinwein (*Z. Naturforsch.*, 1952, **7b**, 270; cf. Schiedt, *ibid.*, 1953, **8b**, 66; Franck, *ibid.*, 1954, **9b**, 276) with a Perkin–Elmer double-beam instrument with rock-salt prism.

Isomerisation of Sarsasapogenin.—Sarsasapogenin [1·5 g. of a commercial product, m. p. 191—198°, $[\alpha]_D^{25}$ −77°, $[\alpha]_{5461}^{25}$ −90° (*c*, 1·2) (infrared absorption as reported by Jones, Katzenellenbogen, and Dobriner, *J. Amer. Chem. Soc.*, 1953, **75**, 158)], was dissolved in 95% ethanol (150 ml.), and a mixture of 95% ethanol (100 ml.) and concentrated hydrochloric acid (45 ml.) was added. Boiling was continued for 96 hr., then a further 40 ml. of hydrochloric acid were added and the mixture was boiled for 24 hr. longer. The product was isolated by addition of water and extraction of the mixture with ether. Evaporation of the washed extract yielded a solid which, recrystallised from acetone, gave 0·42 g. of crystals, m. p. 157—160°, $[\alpha]_D$ − 64° (*c*, 0·48), with the infrared absorption spectrum of smilagenin (C.S. No. 189).* After trials, satisfactory purification was accomplished by conversion into the acetate by acetic anhydride in pyridine and passing a solution of this material (0·3 g.) in benzene through a column (15 × 2 cm.) of neutral alumina. After a trace of oil, a fraction came through which crystallised, on evaporation and rubbing with methanol, in long, silky needles, m. p. 150—153°, not depressing the m. p. of authentic material (m. p. 146—151°), $[\alpha]_D^{19}$ −62°, $[\alpha]_{5461}^{19}$ −71° (*c*, 0·881) (Found: C, 75·9; H, 10·1. Calc. for $C_{29}H_{46}O_4$: C, 75·9; H, 10·1%); the infrared absorption spectrum (C.S. No. 190) was identical with that of authentic material (C.S. No. 191). Authentic smilagenin (8 g.) was prepared from grey Jamaica sarsaparilla (23 kg.) essentially as described by Askew, Farmer, and Kon (*J.*, 1936, 1399). The physical constants of the alcohol and of the acetate agreed with those recorded (*loc. cit.*) and the infrared absorption of the acetate was in agreement with the curves published by Eddy, Wall, and Scott (*Analyt. Chem.*, 1953, **25**, 266) and by Dobriner, Katzenellenbogen, and Jones ("Infrared Absorption Spectra of Steroids. An Atlas," Interscience, New York, 1953).

Fractionation of Sapogenin Acetates from Sisal.—Residues (200 g.), consisting of acetates of

* Infrared spectra thus marked have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained from the General Secretary, the Chemical Society, Burlington House, Piccadilly, London, W.1, on application stating the C.S. No.

mixed sapogenins after collection of most of the hecogenin, derived from Kenya sisal, were boiled under reflux with Girard's reagent T (100 g.) and acetic acid (100 g.) in ethanol (2 l.) for 2 hr. The solution was filtered hot. Material which separated in the filter (fraction A) (10 g.), m. p. 176—190°, consisted of tigogenin acetate, recognisable by the infrared absorption. Fraction B (56 g.), m. p. 168—184°, which separated on cooling, was, judged from the relative height of the absorption bands at 920 and 900 cm.$^{-1}$, a mixture of tigogenin and *neo*tigogenin acetates in about equal amounts; and fraction C (45 g.; m. p. 152—164°), which separated after addition of 2N-sodium carbonate solution (750 ml.) and water (2 l.), was, by the same criterion, mostly *neo*tigogenin acetate. A ketonic fraction (88 g.), m. p. 217—230° (mostly hecogenin acetate), was obtained by acidification of the filtrate from fraction C. The first *neo*tigogenin acetate obtained actually separated from mother-liquors of a non-ketonic acetate fraction in the compact octahedra first described by Goodson and Noller (*loc. cit.*), having m. p. 174—180°, $[\alpha]_D$ −79°, $[\alpha]_{5461}$ −91° (*c*, 0·312). Systematic separation was, however, achieved by fractionation from *iso*propanol. Fraction B was added to the mother-liquors of fraction A and, after collection of the crystals, the mother-liquors were used to recrystallise fraction C. The solid which separated (37·5 g.; m. p. 168—175°) was largely *neo*tigogenin acetate and the m. p. rose to 175—181° on repeated recrystallisation. Hydrolysis of the acetate by sodium hydroxide in aqueous ethanol (15% of H_2O) yielded *neo*tigogenin in thin hexagonal plates, m. p. 197—203°, $[\alpha]_D$ −75°, $[\alpha]_{5461}$ −84° (*c*, 0·659), the infrared absorption spectrum closely matching that given in the literature (Jones *et al.*, and Dobriner *et al.*, *locc. cit.*).

A ketonic fraction obtained as described above from a cruder, yellow, crystallisation residue derived from Jamaica sisal was the source of sisalagenin. This fraction (16·8 g.), recrystallised from *iso*propanol, yielded three successive crops on cooling and evaporation: (*a*) (6 g.) hecogenin acetate, (*b*) (6·3 g.) m. p. 196—200°, with infrared absorption at 918 cm.$^{-1}$ higher than at 897 cm.$^{-1}$ (ratio of heights above intermediate minimum 22/9), and (*c*) (3·2 g.) pasty. Fractional crystallisation of (*b*) with the addition of a fraction from (*c*) yielded, with some careful manipulation in the way of seeding and separating rapidly the first crops of crystals, 1·15 g. of *sisalagenin acetate*, m. p. 226—229°, $[\alpha]_D$ −12°, $[\alpha]_{5461}$ −13° (*c*, 1·05). Recrystallised to constant m. p. from ethanol–light petroleum (b. p. 100—120°) and ethyl acetate, the substance formed prisms, m. p. 228—232°, $[\alpha]_D^{22}$ −12°, $[\alpha]_{5461}^{22}$ −12° (*c*, 1·006) (Found: C, 74·0; H, 9·5. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·5%). The infrared absorption (C.S. No. 192) generally resembles that of hecogenin acetate, but there are differences between 1100 and 950 cm.$^{-1}$, where the strong bands are at 1068, 1038, and 986 cm.$^{-1}$: the "normal" sapogenin characteristics are shown in the much greater height of the band at 918 relative to that at 898 and in the presence of a band at 850 and only a weak maximum at 865 cm.$^{-1}$. Hydrolysis by aqueous-ethanolic sodium hydroxide yielded *sisalagenin*, which formed prisms (from ethyl acetate), m. p. 244—246°, $[\alpha]_D^{22}$ −4·5°, $[\alpha]_{5461}^{22}$ −2° (*c*, 1·408) (Found: C, 75·2; H, 10·2. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). The infrared absorption spectrum (C.S. No. 193) was concordant with that of the acetate, allowing for removal of the acetoxyl group.

pseudo*Sisalagenin*.—Sisalagenin acetate was converted by the method of Cameron, Evans, Hamlet, Hunt, Jones, and Long (*J.*, 1955, in the press) into pseudo*sisalagenin* which separated from acetone in platy crystals, m. p. 188—191° after a transition at about 100°, $[\alpha]_D^{21}$ +92°, $[\alpha]_{5461}^{21}$ +112° (*c*, 0·830) (Found: C, 75·7; H, 10·0%). The infrared absorption spectrum (C.S. No. 194) in potassium chloride was typical of a *pseudo*sapogenin and practically indistinguishable from that of *pseudo*hecogenin (C.S. No. 195), with a prominent, blunt maximum at 1043 cm.$^{-1}$. The band at 1708 cm.$^{-1}$ (CO) obscured the vinyl ether band only indicated by a bulge on the low-frequency side. Acetylation by boiling with acetic anhydride yielded pseudo*sisalagenin diacetate*, plates (from methanol), m. p. 111—113°, $[\alpha]_D^{20}$ +70°, $[\alpha]_{5461}^{20}$ +87° (*c*, 0·453; *l* 2 dm.) (Found: C, 72·4; H, 9·3. $C_{31}H_{46}O_6$ requires C, 72·3; H, 9·0%). The infrared absorption spectrum in potassium chloride (C.S. No. 196) showed the characteristics to be expected from the spectrogram of the alcohol.

Degradation of pseudo*Sisalagenin*.—*pseudo*Sisalagenin (0·43 g.) was dissolved in glacial acetic acid (50 ml.), and to this solution at 22·5° was added a solution of chromic oxide (0·6 g.) in 80% aqueous acetic acid (6 ml.). The temperature rose immediately to 25·5° and some greenish solid appeared. After 1 hr. at room temperature, the solid had dissolved to give a clear solution. Water was then added and the mixture extracted five times with ether. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residual green gum (0·36 g.) was warmed on the steam-bath for 30 min. with N-sodium hydroxide (5 ml.). The alkaline solution was diluted with water and extracted four times with ether. Washed, dried, and evaporated, the ether yielded 0·13 g. of crystals (A). The alkaline liquors from the

extraction were acidified with dilute hydrochloric acid and extracted five times with ether. Drying and evaporation of the ether gave a brown gum (30 mg.) which was sublimed at 100° *in vacuo* to give α-methylglutaric acid (9 mg.), m. p. 70—75° $[\alpha]_D^{22}$ +18° (*c*, 0·9 in EtOH; *l* 1 dm.). The neutral solid (A) was put on an alumina column in benzene. Elution with chloroform–benzene (1 : 4) gave 110 mg. of crystals, which on crystallisation from ether had m. p. 223·5—229° and were identified as *allo*pregn-16-ene-3 : 12 : 20-trione by the infrared absorption spectrum and comparison with an authentic specimen prepared from hecogenin (James, *loc. cit.*). A further few mg. of solid, m. p. 202—222°, was eluted from the column by chloroform–benzene (1 : 1), but was not further investigated.

Isomerisation of Sisalagenin.—Sisalagenin acetate (2·25 g.) was dissolved in boiling ethanol (300 ml.); concentrated hydrochloric acid (50 ml.) was added and boiling continued for 120 hr. Water was added to the boiling solution to precipitate the product, which separated as plates (1·77 g.), m. p. 224—237°, which appeared by the infrared absorption spectrum to consist of hecogenin contaminated with a little sisalagenin. Acetylation (acetic anhydride in pyridine) and purification of the acetate by chromatography on neutral alumina and by crystallisation from *iso*propanol and from petroleum gave a product of m. p. 234—237°, or 237—243° mixed with authentic hecogenin acetate (m. p. 241·5—243°). It had $[\alpha]_D^{22}$ −4°, $[\alpha]_{5461}^{25}$ −3° (*c*, 1·002). The anomalous rotatory dispersion is also found in authentic hecogenin acetate. The free sapogenin obtained by hydrolysis crystallised from light petroleum in elongated plates, m. p. 250—257°, or 257—259° mixed with authentic hecogenin (m. p. 259—260°), $[\alpha]_D^{22}$ +4°, $[\alpha]_{5461}^{22}$ +8° (*c*, 0·661). The infrared absorption spectrum (C.S. No. 197) was similar in every detail to one of authentic hecogenin (C.S. No. 198).

pseudoneo*Tigogenin.*—*neo*Tigogenin acetate was converted into *pseudoneo*tigogenin by the method of Cameron *et al.* (*loc. cit.*). The product formed plates (from acetone), m. p. 180—184° $[\alpha]_D^{21}$ +10°, $[\alpha]_{5461}^{21}$ +13° (*c*, 0·93) (Found: C, 77·8; H, 10·8. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·65%). The infrared absorption spectrum (C.S. No. 199) was almost indistinguishable from that of *pseudo*tigogenin: it was of the usual type for a *pseudo*sapogenin with a blunt maximum at 1040 cm.$^{-1}$ and a peak of medium strength at 1693 cm.$^{-1}$ (C=C·O·).

Degradation of pseudoneo*Tigogenin.*—*pseudoneo*Tigogenin (1 g.) was suspended in ethylene dichloride (10 ml.), and a solution of chromic acid in 90% acetic acid added until excess was present (about 1·5 g. in 30 ml.). After 2 hr. methanol was added to destroy the remaining chromic acid, organic solvent was removed by distillation and steam-distillation, and the product worked up as described previously. The (+)-α-methylglutaric acid obtained (17·6 mg.) had m. p. 74—80°, $[\alpha]_D$ +16·5° (*c*, 0·16 in EtOH), after sublimation. Again crystallised from ether and pentane its m. p. rose to 83—85°.

Isomerisation of neo*Tigogenin.*—*neo*Tigogenin acetate (2·26 g.) was treated with hydrochloric acid in ethanol in the same way as in the isomerisation of sisalagenin (above). The crude product (1·75 g.), m. p. 185—194°, had infrared absorption indicating that it was tigogenin slightly contaminated with *neo*tigogenin. Acetylation and recrystallisation of the acetate from ethyl acetate yielded a product, m. p. 195—202°, m. p. 197—207° when mixed with tigogenin acetate (m. p. 206—209°), $[\alpha]_D^{21}$ −72°, $[\alpha]_{5461}^{21}$ −84° (*c*, 1·121). The infrared absorption spectrum (C.S. No. 200) showed complete similarity in all details with one of authentic tigogenin acetate (C.S. No. 201).

Another isomerisation experiment yielded 4·6 g. of crude tigogenin, m. p. 191—199°; this was converted into the *pseudo*sapogenin which was then oxidised. (−)-α-Methylglutaric acid, m. p. 80—85°, $[\alpha]_D^{20}$ −18° (*c*, 1·11 in EtOH), was separated in the usual way. An authentic specimen of natural tigogenin yielded (−)-α-methylglutaric acid, m. p. 74—82°, $[\alpha]_D$ −16° (*c*, 0·5 in EtOH).

Epimerisation under different conditions was carried out by heating *neo*tigogenin acetate (0·5 g.) in dioxan (80 ml.) and concentrated hydrochloric acid (15 ml.). After 48 hr. on the steam-bath the product was examined and the infrared absorption indicated that it was mostly *neo*tigogenin. However, after a further 64 hr. 0·3 g. of crystals, m. p. 195—198·5°, separated when the solution was cooled, and infrared examination showed an absorption spectrum identical with that of tigogenin. Repetition of this experiment with the addition of acetic anhydride (25 ml.) to the other reagents gave a similar result, the tigogenin which separated having m. p. 194—199° after crystallisation from *iso*propanol, and an infrared absorption spectrum indistinguishable from that of authentic tigogenin.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7.

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Observations on Taraxerol (Skimmiol).

By C. J. W. Brooks.

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The structure assigned to taraxerol by Spring and his collaborators is confirmed in some details, and identity of taraxerol and skimmiol is finally proved. Ready isomerisation of taraxerol epoxide by acid involves a molecular rearrangement.

Taraxerol, $C_{30}H_{50}O$, first isolated from roots of *Taraxacum officinale* (Burrows and Simpson, *J.*, 1938, 2042), was shown to be *iso*olean-14-en-3β-ol by Beaton, Spring, Stevenson, and Stewart (*Chem. and Ind.*, 1954, 1454; 1955, 35) who also achieved its partial synthesis from β-amyrin. Its probable identity with skimmiol, obtained from *Skimmia* species, and much of its chemistry were reported by Takeda and his collaborators (*J. Pharm. Soc. Japan*, 1941, **61**, 117, 506; 1942, **62**, 390; 1943, **63**, 193, 197). On the other hand, Koller, Hiestand, Dietrich, and Jeger (*Helv. Chim. Acta*, 1950, **33**, 1050), working with material (from *Alnus glutinosa*) which appeared (see Table) but was not proved to be identical with the other alcohols mentioned, considered that it was not a 3-hydroxy-derivative, since they could not reduce the derived ketone by the Wolff–Kishner procedure—Takeda (*loc. cit.*, p. 117) found no steric hindrance when he prepared skimmione oxime.

Our work was carried out with skimmiol generously provided by Dr. Takeda. It confirms the structure proposed by Beaton *et al.* Our earlier conclusion (Brooks, *Chem. and Ind.*, 1953, 1178) that the double bond was at position 18 was based specifically on the assumption that no rearrangement occurs in the reaction of taraxerol acetate with selenium dioxide: this was invalidated by the later discovery (Allan, Johnston, and Spring, *J.*, 1954, 1546) of the ready conversion of *iso*oleanane into oleanane derivatives.

	Skimmiol [a]		Taraxerol [b]		Taraxerol [c]	
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$
Alcohol	279—281°	+ 3°	270°	—	282—283°	+ 3°
Acetate	298—299	+14	297	+ 8°	304—305	+ 9
Benzoate	287—289	+36	284	+35	292—293	+37
Ketone	241—243	+12	—	—	240—241	+12
"Oxide" [d]	283—286	+79	—	—	287	+73
Hydrocarbon †	187—190	−21	—	—	184	−24

[a] Takeda, *locc. cit.* [b] Burrows and Simpson, *loc. cit.* [c] Koller *et al.*, *loc. cit.*
[d] See text. † Identified as olean-13-ene in each case.

We have confirmed, by direct comparison, the identity of skimmiol and its benzoate with taraxerol and its benzoate, kindly supplied by Professor E. R. H. Jones, F.R.S.

Takeda had regarded skimmiol as a double-bond isomer of β-amyrin. We noted (Thesis, London, 1952) that this was consistent with the molecular-rotation differences on epimerisation of the hydroxyl group and Takeda's conversion of dihydroskimmiol into the A-nor-ketone (Δ +293°; cf. Klyne, *J.*, 1952, 2916); the same applies to skimmiol and its A-nor-ketone (Δ +402°). Further, in disagreement with Koller *et al.* (*loc. cit.*) we found taraxerone to be readily reduced by the Wolff–Kishner method to taraxerene, $C_{30}H_{50}$, corresponding to Takeda's "skimmiene II*a*" and recently isolated by Bruun (*Acta Chem. Scand.*, 1954, **8**, 1291) from the lichen, *Cladonia deformis*.

Taraxeryl acetate with selenium dioxide gives oleana-11 : 13-dienyl acetate (27%) and 12 : 19-dioxo-oleana-9 : 13-dienyl acetate (5%).

The trisubstituted nature of the ethylenic linkage in taraxerol is consistent with an infrared absorption band at 814 $cm.^{-1}$ (cf. Koller *et al.*, *loc. cit.*) and the ultraviolet absorption at 210—223 mμ (cf. p. 1676).

Taraxerol and its esters smoothly consume one mol. of per-acid, affording well-defined epoxides. These are easily isomerised by acid to unsaturated alcohols: the compound described by Koller *et al.* (*loc. cit.*) as "taraxeryl acetate oxide" and eluted from alumina by benzene–ether (9 : 1) was evidently the isomeric alcohol, the acetate of Takeda's "β-hydroxyskimmiol" (see Table). This is not an allylic alcohol, since the corresponding

diketone, prepared by chromic acid oxidation, and reducible back to the alcohol (Takeda, *loc. cit.*, p. 390), shows no high-intensity absorption in the ultraviolet ($\lambda_{max.}$ 295 mμ, ε 67); similarly the monoketone " β-ketoskimmiol acetate " exhibits only the band at 300 mμ (ε 40) expected for a saturated ketone. It is thus clear that the isomerisation of the epoxides under the influence of acids is accompanied by a molecular rearrangement, doubtless of carbonium-ion type.

Experimental

M. p.s taken on a Kofler stage are indicated by (K). Optical rotations were determined in $CHCl_3$ at room temperature (15—25°). Ultraviolet absorption spectra were measured in ethanol solution with a Unicam S.P. 500 Spectrophotometer. " Neutralised alumina " was prepared by treatment with ethyl acetate overnight, followed by exhaustive washing with water and reactivation at 200°. Light petroleum refers to the fraction of b. p. 40—60°.

Taraxerol crystallised from benzene–hexane as needles, m. p. 278—280° (K), $[\alpha]_D$ +2° (*c*, 1·32). Light absorption: 210 (ε 3900), 215 (ε 2400), 220 (ε 700), and 223 mμ (ε 250).

Taraxeryl acetate crystallised from benzene as large prisms, m. p. 303—307° (K), giving a very pale yellow colour with tetranitromethane. The infrared spectrum in Nujol mull revealed a band at 814 $cm.^{-1}$: this determination was kindly made by Dr. J. E. Page.

Taraxeryl Benzoate.—Taraxerol (132 mg.), chloroform (5 ml.), pyridine (1 ml.), and benzoyl chloride (0·5 ml.) were mixed and left at room temperature overnight. The usual working up afforded a crude product which was dissolved in benzene and filtered through alumina, yielding on evaporation the benzoate (167 mg.) which formed glittering prisms (121 mg.), m. p. 282—288°, $[\alpha]_D$ +34° (*c*, 0·98), from chloroform–methanol. One further recrystallisation raised the m. p. to 288—289°. To test the homogeneity of the taraxerol, a sample (1·05 g.) was benzoylated affording 727 mg. of pure benzoate. The mother-liquor was evaporated and the residue (550 mg.) chromatographed on alumina (Savory and Moore; 30 g.). Practically all the material (486 mg.) was eluted in one band by light petroleum–benzene (1 : 1) and had $[\alpha]_D$ +34° (*c*, 1·00).

Taraxerone.—When prepared according to Koller *et al.* (*loc. cit.*) and recrystallised from chloroform–methanol, this had m. p. 245—249° (K), $[\alpha]_D$ +12° (*c*, 1·38), and gave a strong purple colour in the Zimmermann test (Barton and de Mayo, *J.*, 1954, 887).

Taraxerene.—A mixture of taraxerone (50 mg.) suspended in ethanol (0·5 ml.), hydrazine (0·6 ml.), and sodium (125 mg.) dissolved in ethanol (1·3 ml.) was heated for 18 hr. at 200°. Working up as usual gave a crude product (47 mg.) which was chromatographed in light petroleum on alumina (Savory and Moore; 2 g.). The first 25 ml. of eluate afforded taraxerene (34 mg.), m. p. 238—243°, $[\alpha]_D$ +3° (*c*, 0·68), sparingly soluble (about 1% at 25°) in chloroform, from which it crystallised as large hexagonal plates, m. p. 238—240°. A sample sublimed in a high vacuum had the same m. p. (Found: C, 87·8; H, 12·2. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%).

Taraxerol Oxide.—A solution of taraxerol (364 mg.) in " AnalaR " chloroform (20 ml.) was treated with a solution (50 ml.; 0·025M) of monoperphthalic acid in ether and left in the dark at room temperature for 3½ days. Titration indicated that approx. 80% of the required amount of oxidant had been consumed. Working up in the usual way afforded a crude product which, after removal of a substance sparingly soluble in acetone, crystallised from aqueous acetone to give taraxerol oxide as long prisms (178 mg.), m. p. 204—208° (K), $[\alpha]_D$ +33° (*c*, 1·00).

Taraxeryl acetate oxide, prepared similarly (92% of the required uptake of peracid), was purified by chromatography on neutralised alumina. Light petroleum–benzene (1 : 1) eluted the oxide, which formed plates, m. p. 245—247° (K), from chloroform–methanol, $[\alpha]_D$ +51° (*c*, 0·93), and gave no colour with tetranitromethane (Found: C, 79·2; H, 10·65. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%).

Action of Selenium Dioxide on Taraxeryl Acetate.—The acetate (200 mg.) in " AnalaR " acetic acid (75 ml.) was refluxed for 20 hr. with selenium dioxide (100 mg.). Working up in the usual way afforded a crude product (207 mg.) which was chromatographed on neutralised alumina (7 g.). Two main crystalline fractions were obtained: (i) eluted by light petroleum–benzene (9 : 1) amounted to 136 mg., (ii) eluted by benzene–ether (95 : 5) amounted to 19 mg. Fraction (i), recrystallised from chloroform–methanol, gave prisms (26 mg.), m. p. 304—305°, identified as taraxeryl acetate (mixed m. p.). Fractional crystallisation from the mother-liquor afforded 55 mg. of a compound crystallising as plates (from ethyl acetate–methanol), m. p. 226—227° (K), $[\alpha]_D$ −58° (*c*, 1·94), $\lambda_{max.}$ 242, 250, and 259·5 mμ (log ε 4·35, 4·4, and 4·2) giving no depression in m. p. on admixture with oleana-11 : 13-dienyl acetate (Ruzicka and Jeger, *Helv.*

Chim. Acta, 1941, **24**, 1236) of the same m. p., $[\alpha]_D$ −68°. Fraction (ii), recrystallised from aqueous methanol, formed dense quadrilateral tablets (11 mg.), m. p. 237—240° (K), $[\alpha]_D$ −90° (*c*, 0·60), $\lambda_{max.}$ 276 mμ (log ε 4·07), undepressed in m. p. on admixture with 12 : 19-dioxo-oleana-9 : 13-dienyl acetate of similar crystal form and m. p., $[\alpha]_D$ −94° (*c*, 1·16).

Isomerisation of Taraxerol Oxide.—Taraxerol oxide (148 mg.) was refluxed for 3 hr. in ethanol (50 ml.) containing aqueous 2·5N-sulphuric acid (2 ml.). Working up in the usual way furnished a crude product which crystallised from aqueous acetone as fine needles (75 mg.), m. p. 240—242° (K). Sublimation in a high vacuum gave rectangular prisms, m. p. 244—245° (K), $[\alpha]_D$ +83° (*c*, 0·69), of " β-hydroxyskimmiol."

Isomerisation of Taraxeryl Acetate Oxide.—Taraxeryl acetate oxide (500 mg.) was heated for 3 hr. on the steam-bath with acetic acid (80 ml.) containing aqueous 4N-hydrochloric acid (2 ml.). Working up in the usual way gave, after crystallisation from benzene, prisms (300 mg.), m. p. 279—282° (K), $[\alpha]_D$ +75° (*c*, 1·07), of " β-hydroxyskimmiol acetate."

Chromic Acid Oxidation of " β-Hydroxyskimmiol."—" β-Hydroxyskimmiol " (54 mg.) in acetic acid (30 ml.) was treated dropwise with a solution (5 ml.) of chromium trioxide (3·75 mg./ml.) in 99% acetic acid. The solution became green in a few hours. Working up in the usual way gave a crude product (52·5 mg.) which was chromatographed on neutralised alumina (2 g.). Light petroleum–benzene (9 : 1) eluted crystalline material (26 mg.), m. p. 208—212° (K), raised by recrystallisation from methanol to 210—213° (K), $[\alpha]_D$ +29° (*c*, 0·82), $\lambda_{max.}$ 295 mμ (ε 67) (Found : C, 82·0; H, 10·4. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%). There was no high-intensity absorption in the ultra-violet above 220 mμ.

Chromic Acid Oxidation of " β-Hydroxyskimmiol Acetate."—" β-Hydroxyskimmiol acetate " (51 mg.), partly dissolved in acetic acid (15 ml.), was treated with a solution (5 ml.) of chromium trioxide (0·065N) in acetic acid and shaken for 20 min. A clear solution was formed, and titration of an aliquot portion indicated that 120% of the required amount of oxidant (for one secondary hydroxyl group) had been consumed. Working up in the usual way and crystallisation of the product from benzene–light petroleum gave prisms (23 mg.), m. p. 274—276°, $[\alpha]_D$ +15° (*c*, 0·96). In a second preparation the product was entirely eluted from alumina (Savory and Moore) by light petroleum–benzene (1 : 1) and had, when recrystallised from benzene–light petroleum, m. p. 274—277°, $[\alpha]_D$ +15° (*c*, 0·91), $\lambda_{max.}$ 300 mμ (ε 40). Takeda (*loc. cit.*, p. 390) gave $[\alpha]_D$ +4°, while Beaton *et al.* (*Chem. and Ind.*, 1954, 1454) reported $[\alpha]_D$ +27°.

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The Preparation of Some N-*Alkyl-* *and* NN-*Dialkyl*-p-*nitrosoanilines.*

By J. WILLENZ.

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Preparation of a number of *N*-alkyl- and *NN*-dialkyl-*p*-nitrosoanilines is described. Attempted Fischer–Hepp rearrangement of *N*-nitroso-*N*-*n*-octadecylaniline results in denitrosation. No difficulty was experienced in direct introduction of a *p*-nitroso-group into any dialkylanilines, even those with bulky substituents.

A SERIES of *p*-nitrosoanilines has been prepared after the observation that *p*-nitrosoaniline and a number of its derivatives in which the amino-group is alkylated with very small alkyl groups showed high activities *in vitro* as fungicides and as bactericides against a wide range of test organisms. These biological results will be reported elsewhere.

As expected, nitrosation of *N-iso*propylaniline followed by Fischer–Hepp rearrangement of the *N*-nitroso-derivative (*Ber.*, 1886, **19**, 2991) gave the *p*-nitroso-compound, *via* the hydrochloride, without difficulty. *N-n*-Hexylaniline, which was preferably obtained in a pure state by a one-stage process from excess of aniline and hexyl bromide (cf. Hickinbottom, *J.*, 1937, 1119), readily gave the *N*-nitroso-compound, but rearrangement gave poor yields of *N-n*-hexyl-*p*-nitrosoaniline.

3 : 5 : 5-Trimethylhexylaniline was prepared pure by prolonged treatment of a large excess of aniline with 3 : 5 : 5-trimethylhexyl iodide in light petroleum. The autoclave method of Reilly and Hickinbottom (*J.*, 1918, **113**, 99) using aniline hydrochloride and 3 : 5 : 5-trimethylhexanol gave no material corresponding to either mono- or di-alkylated aniline. Nitrosation of the base in the usual way gave *N*-nitroso-*N*-(3 : 5 : 5-trimethylhexyl)aniline in good yield which was rearranged to the corresponding *p*-nitroso-compound in 33% yield.

N-*n*-Octadecylaniline was described by Adler, Haskelberg, and Bergmann (*J.*, 1940, 576). Nitrosation of the pure base gave the *N*-nitroso-derivative, but attempts to rearrange the latter always resulted in denitrosation to *N*-*n*-octadecylaniline hydrochloride. Steric hindrance could be the explanation for the failure of the Fischer–Hepp rearrangement here. Inspection of the Stuart model shows that the aliphatic chain is sufficiently long to coil around the aromatic ring in such a way as to block not only the *para*-position but also any position of the benzene nucleus. Hickinbottom (*J.*, 1933, 946) similarly made unsuccessful attempts to prepare *N*-*tert.*-butyl-*p*-nitrosoaniline by the action of solutions of hydrogen chloride in alcohol or acetic acid on the *N*-nitroso-amine, the hydrochloride of *tert.*-butylaniline being the principal product.

Crossley, Turner, Hofmann, Dreisbach, and Parker (*J. Amer. Chem. Soc.*, 1952, **74**, 578) failed to prepare *p*-nitroso-*NN*-di*iso*propylaniline and explained this on steric grounds, citing Hickinbottom's reports of an unsuccessful attempt (*J.*, 1933, 946) to nitrosate *N*-methyl-*N*-*tert.*-butylaniline. It has also been claimed that the reaction fails if the alkyl groups are large (see Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1942, p. 218). However, in the present work *NN*-dialkyl-*p*-nitrosoanilines were successfully prepared by the direct introduction of the *p*-nitroso-group into the appropriate dialkylaniline and no difficulty has been experienced in the preparation of several heavily substituted dialkyl-*p*-nitrosoanilines.

NN-Di-*n*-hexylaniline (orginally prepared by Slotta and Franke, *Ber.*, 1933, **66**, 104) was obtained by prolonged heating of 2 mols. of *n*-hexylaniline and 1 mol. of hexyl bromide in light petroleum. Nitrosation gave *NN*-di-*n*-hexyl-*p*-nitrosoaniline, which was characterised by reduction to the corresponding *p*-phenylenediamine and this with 1-chloro-2 : 4-dinitrobenzene gave 4-di-*n*-hexylamino-2' : 4'-dinitrodiphenylamine.

N-*n*-Hexyl-*N*-methylaniline was obtained in good yield from *N*-methylaniline and *n*-hexyl bromide. This gave *N*-*n*-hexyl-*N*-methyl-*p*-nitrosoaniline, and thence the corresponding diamine.

Prolonged refluxing of 2 mols. of *N*-3 : 5 : 5-trimethylhexylaniline with 1 mol. of 3 : 5 : 5-trimethylhexyl iodide in light petroleum gave the dialkylaniline in good yield. This readily gave the *p*-nitroso-compound, the diamine, and 4-*NN*-bis-(3 : 5 : 5-trimethylhexyl)amino-2' : 4'-dinitrodiphenylamine.

A superior synthesis of *N*-methyl-*N*-3 : 5 : 5-trimethylhexylaniline was devised (see de Benneville and Macartney, *J. Amer. Soc.*, 1950, **72**, 3073). Conditions for nitrosating this compound were critical. The *p*-nitroso-compound gave a derivative with picrolonic acid that although of sharp m. p. gave unsatisfactory analytical data. Reduction of the hydrochloride of the *p*-nitroso-compound, however, gave the corresponding *p*-phenylenediamine which led to 4-(*N*-methyl-*N*-3 : 5 : 5-trimethylhexylamino)-2' : 4'-dinitrodiphenylamine. Analogously, the *N*-ethyl-*N*-3 : 5 : 5-trimethylhexylaniline was prepared, but, whereas the *N*-methyl compound gave a stable and well-defined picrolonate, this compound gave an ill-informed adduct with picrolonic acid for which analytical results were never satisfactory. Nitrosation of the *N*-ethyl analogue was carried out normally, and the product reduced and converted into the dinitrodiphenylamine derivative.

Experimental

p-*Nitroso*-N-iso*propylaniline*.—*N-iso*Propylaniline (b. p. 204—207°; 10 g.) in concentrated hydrochloric acid (10·75 c.c.) was nitrosated in the usual way with a solution of sodium nitrite (5·33 g.) in water (18·5 c.c.). Ether-extraction and evaporation of the dried extract gave *N*-nitroso-*N-iso*propylaniline as a yellow oil; it was dissolved in dry ether (25 c.c.) and absolute

alcohol (60 c.c.) which was saturated with hydrogen chloride. The mixture was set aside for *ca.* 1½ hr. at room temperature and the hydrochloride of *p*-nitroso-*N*-*iso*propylaniline was then precipitated on addition of more ether. It was collected and treated with an excess of aqueous ammonia, and the free base extracted with ether. Evaporation of the dried ether extract gave pure p-*nitroso*-N-*isopropylaniline*, bluish-green crystals of metallic lustre (3·1 g., 25·4%), m. p. 82·5° (decomp.), not increased after recrystallization from light petroleum (b. p. 60—80°) (Found: C, 65·6; H, 7·7; N, 17·0. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·33; N, 17·1%).

While this work was in progress Crossley *et al.* (*loc. cit.*) reported the preparation of *p*-nitroso-*N*-*iso*propylaniline as a green solid, m. p. 53·3—53·7°. Independent preparation of this compound in these laboratories by Dr. C. Wickham Jones gave greenish-blue crystals (from ethyl acetate and light petroleum, b. p. 40—60°), m. p. 86°. The mixed m. p. of the latter sample with a sample described above (m. p. 82·5°) was 84—85°.

N-n-*Hexylaniline*.—Aniline (100 g.) was refluxed with *n*-hexyl bromide (55 g.) in light petroleum (b. p. 60—80°; 30 c.c.) for 39 hr. The mixture was poured into water, treated with an excess of aqueous ammonia, and extracted with ether. The washed (H_2O) and dried (Na_2SO_4) ether extract was filtered, the solvent evaporated, and the residual oil fractionally distilled *in vacuo*. *N*-*n*-Hexylaniline was obtained as a pale yellow oil, b. p. 94—101°/0·7—1 mm., n_D^{20} 1·5223 [Found: C, 81·3; H, 10·7; N, 7·9%; *M* (cryoscopic in benzene), 172 ± 5. Calc. for $C_{12}H_{19}N$: C, 81·4; H, 10·7; N, 7·8%; *M*, 177]. The toluene-*p*-sulphonyl derivative had m. p. 63—64° (Hickinbottom, *J.*, 1937, 1119, gives 67—68°) (Found: C, 68·8; H, 7·6; N, 4·5. Calc. for $C_{19}H_{25}O_2NS$: C, 68·9; H; 7·6; N, 4·2%). The pale yellow *picrolonate* had m. p. 160—161·5° (from ether) (Found: C, 60·0; H, 6·0; N, 15·7. $C_{22}H_{27}O_5N_5$ requires C, 59·8; H, 6·1; N, 15·9%). *N*-*n*-Hexylaniline did not give a solid hydrochloride in dry ether or light petroleum (b. p. 40—60°).

N-n-*Hexyl*-N-*nitrosoaniline*.—*N*-*n*-Hexylaniline (10 g.) did not dissolve in concentrated hydrochloric acid (33 c.c.) at 0°; even when hydrogen chloride was bubbled through the mixture, complete dissolution was not obtained. The mixture was nitrosated with an aqueous solution (14·2 c.c.) of sodium nitrite (4·07 g.) in the usual way and worked up as described for *N*-nitroso-*N*-*iso*propylaniline. N-n-*Hexyl*-N-*nitrosoaniline* (9·27 g., 80%) was obtained as an amber-coloured, viscous oil, b. p. 127—130°/1·5 mm. [Found: C, 69·8; H, 8·6; N, 13·5%; *M*, 198 (cryoscopic in benzene). $C_{12}H_{18}ON_2$ requires C, 69·9; H, 8·75; N, 13·6%; *M*, 206].

N-n-*Hexyl*-p-*nitrosoaniline*.—(*a*) *N*-*n*-Hexyl-*N*-nitrosoaniline (7·95 g.) in dry ether was treated with dry pure methanol (60 c.c.) which was saturated with dry hydrogen chloride. Adding a very large amount of dry ether and passing further dry hydrogen chloride through the solution precipitated a solid after several hours' storage. This was collected, dissolved in aqueous ammonia, and extracted with ether, and the dried extract evaporated. Three recrystallisations of the residual material from benzene–light petroleum (b. p. 40—60°) gave N-n-*hexyl*-p-*nitrosoaniline* as blue crystals with a metallic lustre, m. p. 47—48° (0·58 g., 7·2%) (Found: C, 69·8; H, 9·1; N, 13·1%; *M*, 202 ± 10. $C_{12}H_{18}ON_2$ requires C, 69·9; H, 8·8; N, 13·6%; *M*, 206). (*b*) Methanol (12 c.c.) and ether (30 c.c.), both saturated in the cold with dry hydrogen chloride, were added to *N*-*n*-hexyl-*N*-nitrosoaniline (*ca.* 8 g.), and the solution kept a room temperature for 2 hr. No solid was precipitated; the solution was evaporated *in vacuo* (water-bath). The residual orange-coloured, viscous oil was treated with an excess of aqueous potassium carbonate and extracted with ether, and the washed and dried (Na_2SO_4) extract evaporated. The residual oil was extracted with boiling light petroleum (b. p. 40—60°, or 60—80°) from which *N*-*n*-hexyl-*p*-nitrosoaniline was obtained on cooling (1·19 g., *ca.* 15%; crude, m. p. 41—42°). The *picrolonate*, m. p. 133·5° (decomp.), was obtained from ether as a light brown powder. Although this was sparingly soluble in ether, the ether solution had to be evaporated to very small bulk before crystallisation occurred (Found: C, 55·8; H, 5·4; N, 17·7. $C_{23}H_{26}O_6N_6$ requires C, 56·2; H, 5·5; N, 17·9%).

N-3 : 5 : 5-*Trimethylhexylaniline*.—3 : 5 : 5-Trimethylhexyl iodide [freshly prepared (cf. Jones and Whitfield, *J.*, 1953, 2795); b. p. 62°/2 mm., 50·8 g.] and aniline (freshly distilled; 60 g.) in light petroleum (b. p. 60—80°; 25 c.c.) were refluxed for 30 hr. and the product was worked up as described for *N*-*n*-hexylaniline. N-3 : 5 : 5-*Trimethylhexylaniline* (b. p. 108—112°/0·5 mm., 310°/760 mm., n_D^{20} 1·5110; 32·8 g., 75%) was obtained as a colourless oil (Found, for material of b. p. 110°/0·5 mm.: C, 82·1; H, 11·5; N, 6·4. $C_{15}H_{25}N$ requires C, 82·2; H, 11·4; N, 6·4%).

N-*Nitroso*-N-3 : 5 : 5-*trimethylhexylaniline*.—Nitrosation of *N*-3 : 5 : 5-trimethylhexylaniline, carried out in the usual way with a 25% excess of aqueous sodium nitrite, gave after distillation of the washed and dried ether extract N-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline* as a yellow oil,

b. p. 126—128°/0·7 mm., n_D^{20} 1·5164 in a yield of 86% (Found: C, 72·7; H, 9·8; N, 11·7. $C_{15}H_{24}ON_2$ requires C, 72·6; H, 9·7; N, 11·3%).

p-*Nitroso*-N-3 : 5 : 5-*trimethylhexylaniline*.—*N*-Nitroso-*N*-3 : 5 : 5-trimethylhexylaniline (b. p. 142—145°/1 mm.; 35·76 g.) in dry ether (70 c.c.), treated with pure methanol (50 c.c.) which had been previously saturated with dry hydrochloric acid, was kept for 4 hr. at room temperature. Subsequent addition of a large amount of dry ether precipitated the yellow hydrochloride of *p*-nitroso-*N*-3 : 5 : 5-trimethylhexylaniline. This was filtered off and suspended in aqueous ammonia which gave the crude blue p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline* (11·7 g., 33% yield), which was collected and purified by several recrystallisations from light petroleum (b. p. 40—60°), to give green crystals, m. p. 93—94° (Found: C, 72·6; H, 9·8; N, 11·6. $C_{15}H_{24}ON_2$ requires C, 72·6; H, 9·7; N, 11·3%). It gave a yellowish-green *picrate*, m. p. 93·5° (Found: C, 52·4; H, 5·7; N, 14·3. $C_{21}H_{27}O_8N_5$ requires C, 52·8; H, 5·7; N, 14·7%). On admixture with *p*-nitroso-*N*-3 : 5 : 5-trimethylhexylaniline, the m. p. was depressed to 59°. The crude addition compound obtained from the *p*-nitroso-compound with 2 : 4-dinitrophenol in ethanol had m. p. 70—74°; the m. p. was lowered after each subsequent crystallisation from ethanol, giving 68·5°, 60—62°, 52—58° successively.

N-n-*Octadecylaniline*.—*n*-Octadecyl bromide (66·6 g.) and aniline (47 g.) in light petroleum (b. p. 60—80°; 30 c.c.) were refluxed for 40 hr. The product was poured into aqueous ammonia and extracted with ether. The washed (H_2O) extract was dried ($MgSO_4$), filtered, and concentrated. The residual brown oil was distilled to give *N*-*n*-octadecylaniline (35·3 g., 51%), m. p. 51—51·5°, b. p. 215—220°/1 mm. Recrystallisation from acetone gave m. p. 51·5° (Bergmann *et al.*, *loc. cit.*, gave m. p. 42°, b. p. 196°/0·6 mm.) (Found: C, 83·5; H, 12·3; N, 4·1. Calc. for $C_{24}H_{43}N$: C, 83·5; H, 12·4; N, 4·1%).

N-*Nitroso*-N-n-*octadecylaniline*.—*N*-*n*-Octadecylaniline (5 g.) in glacial acetic acid (75 c.c.) was nitrosated in suspension at about 5° with vigorous stirring with sodium nitrite (5 g.) in water (8 c.c.). Crystallisation of the crude product (m. p. 48·5—49·5°), obtained in theoretical yield, from methanol gave N-*nitroso*-N-n-*octadecylaniline*, m. p. 50°, as pale yellow needles (Found: C, 77·0; H, 11·2; N, 7·6. $C_{24}H_{42}ON_2$ requires C, 77·0; H, 11·2; N, 7·5%). Admixture with pure *N*-*n*-octadecylaniline (m. p. 51·5°) depressed the m. p. to 41—46°.

Attempted Fischer–Hepp rearrangement. (*a*) The *N*-nitroso-compound (5 g.) in dry ether (20 c.c.) was treated with methanol (10 c.c.) which had been saturated with dry hydrogen chloride. A yellow solid (5·3 g.), the *hydrochloride* of *N*-*n*-octadecylaniline, was immediately precipitated (m. p. 103—103·5°). The m. p. was not raised by recrystallisation from methanol which gave pale yellow, lustrous plates (Found: C, 75·6; H, 11·4; N, 3·8; Cl, 9·2. $C_{24}H_{44}NCl$ requires C, 75·5; H, 11·5; N, 3·7; Cl, 9·3%). The m. p. was not depressed on admixture with a specimen (m. p. 103°) obtained by treating a light petroleum (b. p. 60—80°) solution of *n*-octadecylaniline with dry hydrogen chloride.

(*b*) The hydrochloride was also obtained when *N*-nitroso-*n*-octadecylaniline (2 g.) in glacial acetic acid (15 c.c.) was treated with glacial acetic acid (20 c.c.) saturated with dry hydrogen chloride. Some solid was precipitated immediately and more came down in a few minutes (total, 1·8 g.).

(*c*) *N*-Nitroso-*n*-octadecylaniline (2·5 g.) was dissolved in toluene (40 c.c.) which was saturated with hydrogen chloride. After 4 hr. the brown solution deposited a yellow solid (0·15 g.; m. p. 90°), and adding ether precipitated more material (2 g.; m. p. 89°) which, after recrystallisation from methanol, gave the pure hydrochloride, m. p. 103°.

NN-*Di*-n-*hexylaniline*.—*N*-*n*-Hexylaniline (50 g.) was refluxed with *n*-hexyl bromide (23·3 g.) in light petroleum (b. p. 60—80°) for 48 hr. and worked up as described for the preparation of *N*-*n*-hexylaniline. *NN*-Di-*n*-hexylaniline (21·83 g., 59·3% calc. on hexyl bromide), b. p. 130—135°/0·5 mm. (Slotta and Franke, *loc. cit.*, give b. p. 300—301°/755 mm., 172—173°/15 mm.), n_D^{20} 1·5067 (Found: C, 82·7; H, 12·0; N, 5·6. Calc. for $C_{18}H_{31}N$: C, 82·7; H, 11·9; N, 5·4%), did not give a solid hydrochloride in dry ether when dry hydrogen chloride was passed through it. On evaporation of the solvent a viscous oil was obtained which solidified to a colourless solid, m. p. 101—109°, which was not further purified. A picrate could not be obtained, and the *picrolonate* only could be obtained pure by treating equimolecular proportions of the aniline and picrolonic acid; it formed yellow crystals (from ether), m. p. 108—110° (Found: C, 63·9; H, 7·4; N, 13·2. $C_{28}H_{39}O_5N_5$ requires C, 64·0; H, 7·4; N, 13·3%).

NN-*Di*-n-*hexyl*-p-*nitrosoaniline*.—*NN*-Di-*n*-hexylaniline (4 g.), dissolved in glacial acetic acid (40 c.c.) and concentrated hydrochloric acid (5 c.c.), was nitrosated with stirring with aqueous (5 c.c.) sodium nitrite (1·41 g.) within 8 min. at 2·5—6°. The mixture was treated immediately with an excess of aqueous potassium carbonate and extracted with light petroleum

(b. p. 40—60°), and the dried (Na_2SO_4) extract was evaporated. The residue solidified to a green crystalline mass on strong cooling (solid carbon dioxide–methanol) and scratching but liquefied again at room temperature. NN-*Di*-n-*hexyl*-p-*nitrosoaniline* was purified by repeatedly freezing out from its light petroleum (b. p. 40—60°) solution. At room temperature it is a very viscous oil with a greenish-blue sheen [Found, for material dried at 50° in a high vacuum: C, 74·3; H, 10·2; N, 9·8%; *M* (cryoscopic in benzene), 336 ± 20. $C_{18}H_{30}ON_2$ requires C, 74·5; H, 10·3; N, 9·7%; *M*, 290].

4-*Di*-n-*hexylamino*-2′:4′-*dinitrodiphenylamine*.—Reduction of *NN*-di-*n*-hexyl-*p*-nitrosoaniline (1·19 g.) with zinc dust and hydrochloric acid (cf. Reilly and Hickinbottom, *loc. cit.*) gave the corresponding crude *p*-phenylenediamine (0·8 g.) which was condensed in hot alcohol with 1-chloro-2:4-dinitrobenzene (0·59 g.) to give, after crystallisation from alcohol and subsequently light petroleum, orange crystals of 4-*di*-n-*hexylamino*-2′:4′-*dinitrodiphenylamine*, m. p. 74·5—75° (Found: C, 65·0; H, 7·7; N, 12·7. $C_{24}H_{34}O_4N_4$ requires C, 65·2; H, 7·7; N, 12·7%).

N-n-*Hexyl*-N-*methylaniline*.—*N*-Methylaniline (71·2 g.) was refluxed in light petroleum (b. p. 60—80°; 25 c.c.) with *n*-hexyl bromide (55 g.) for 3 days and the product worked up as described under *N*-*n*-hexylaniline, to give N-n-*hexyl*-N-*methylaniline* (44·6 g., 70·5%), as a practically colourless oil, b. p. 94—98°/0·3 mm., n_D^{20} 1·5229 (Found: C, 81·9; H, 10·8; N, 7·5%; *M*, 181 ± 6. $C_{13}H_{21}N$ requires C, 81·7; H, 11·0; N, 7·3%; *M*, 191).

N-n-*Hexyl*-N-*methyl*-p-*nitrosoaniline*.—*N*-Hexyl-*N*-methylaniline (3·64 g.) in acetic acid (36·5 c.c.) and concentrated hydrochloric acid (4 c.c.) was nitrosated at 3—4° by adding saturated aqueous sodium nitrite (4·5 c.c.) during 7 min. The mixture was then kept for 4—5 min.; its temperature rose to 7°. It was worked up as described under *NN*-di-*n*-hexyl-*p*-nitrosoaniline to give 3·79 g. (90·5%) of a greenish-blue oil which solidified on cooling (solid carbon dioxide–methanol). After freezing out from the dried (Na_2SO_4) light petroleum solution (b. p. 40—60°), N-n-*hexyl*-N-*methyl*-p-*nitrosoaniline* was obtained as bright green needles, m. p. 33·5—34° (Found: C, 70·5; H, 9·1; N, 12·7. $C_{13}H_{20}ON_2$ requires C, 70·9; H, 9·1; N, 12·7%). The *picrolonate*, m. p. 108—109° (decomp.), was obtained as a pale brown solid from aqueous methanol (Found: C, 56·4; H, 6·2; N, 17·4. $C_{23}H_{28}O_6N_6$ requires C, 57·0; H, 5·8; N, 17·4%). Reduction of the *p*-nitroso-compound with zinc dust in hydrochloric acid (cf. Reilly and Hickinbottom, *loc. cit.*) gave the crude *N*-*n*-hexyl-*N*-methyl-*p*-phenylenediamine which was converted into the yellow *picrolonate*, m. p. 141—142° (decomp.) (from chloroform and light petroleum) (Found: C, 58·7; H, 6·6; N, 17·9. $C_{23}H_{30}O_5N_6$ requires C, 58·7; H, 6·7; N, 17·9%).

NN-*Bis*-(3:5:5-*trimethylhexyl*)*aniline*.—Refluxing *N*-3:5:5-trimethylhexylaniline (2 equivs.) with 3:5:5-trimethylhexyl iodide (1 equiv.) in light petroleum and working up as described in the preparation of *N*-*n*-hexylaniline gave NN-*bis*-(3:5:5-*trimethylhexyl*)*aniline* (77·5%), b. p. 150°/0·5 mm., n_D^{20} 1·4961, as a straw-coloured, moderately viscous oil (Found: C, 83·4; H, 12·6; N, 4·2. $C_{24}H_{43}N$ requires C, 83·5; H, 12·5; N, 4·1%). The *monopicrate* was obtained as yellow needles [from light petroleum (b. p. 40—60°)], m. p. 109° (Found: C, 62·5; H, 8·1; N, 10·1. $C_{30}H_{46}O_7N_4$ requires C, 62·7; H, 8·0; N, 9·8%).

p-*Nitroso*-NN-*bis*-(3:5:5-*trimethylhexyl*)*aniline*.—Nitrosation of *NN*-bis-(3:5:5-trimethylhexyl)aniline (5 g.) in acetic acid (25 c.c.) and concentrated hydrochloric acid (5 c.c.) with sodium nitrite (3 g.) in water (7 c.c.) gave after basification with sodium carbonate solution a green oil. This solidified after extraction with light petroleum, washing, drying, and evaporation of the extract (m. p. 44—46°; 2·8 g., 52%). After final purification from light petroleum (b. p. 40—60°), the p-*nitroso-compound* was obtained as green crystals, m. p. 48—48·5° (Found: C, 76·8; H, 11·1; N, 7·7. $C_{24}H_{42}ON_2$ requires C, 77·0; H, 11·2; N, 7·5%). A picrate or a picrolonate could not be obtained.

4-*Bis*-(3:5:5-*trimethylhexyl*)*amino*-2′:4′-*dinitrodiphenylamine*.—Reduction of the preceding compound as above gave *NN*-bis-(3:5:5-trimethylhexyl)-*p*-phenylenediamine as a brown oil in theoretical yield. This was coupled in alcohol with an equimolecular amount of 1-chloro-2:4-dinitrobenzene, to give after recrystallisation from alcohol crimson needles, m. p. 91·5° of 4-*bis*-(3:5:5-*trimethylhexyl*)*amino*-2′:4′-*dinitrodiphenylamine* (Found: C, 68·0; H, 8·6; N, 10·9. $C_{30}H_{46}O_4N_4$ requires C, 68·5; H, 8·7; N, 10·6%).

N-*Methyl*-N-3:5:5-*trimethylhexylaniline*.—This was prepared from methylaniline (45 g.) and 3:5:5-trimethylhexyl iodide (50·8 g.) in light petroleum (b. p. 60—80°; 15 c.c.) and worked up as described for the preparation of *N*-*n*-hexylaniline, giving N-*methyl*-N-3:5:5-*trimethylhexylaniline* as a yellow oil, b. p. 136—140°/2—2·5 mm. (40·7 g., 88%) (Found, for material, b. p. 138°/2 mm., n_D^{20} 1·5108: C, 82·4; H, 11·7; N, 6·1. $C_{16}H_{27}N$ requires C, 82·4;

H, 11·6; N, 6·0%). The *picrolonate* was obtained as canary-yellow crystals, m. p. 133·5—135°, after several recrystallisations from ether (Found: C, 62·7; H, 7·3; N, 13·9. $C_{28}H_{33}O_5N_5$ requires C, 62·8; H, 7·0; N, 14·1%).

N-*Methyl*-p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline*.—*N*-Methyl-*N*-3 : 5 : 5-trimethylhexylaniline (8·7 g.) in concentrated hydrochloric acid (10 c.c.), water (10 c.c.), and glacial acetic acid (20 c.c.) was nitrosated at 0° (±2°) with sodium nitrite (3·5 g., theor., 2·58 g.) in water (10 c.c.) during 20 min. with stirring. The nitrite solution was run under the surface of the liquid. Stirring was continued for a further 20 min. The dark red solution was made alkaline with potassium carbonate and the green viscous oil which separated immediately extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), filtered, and evaporated. The residual oil gave, on strong cooling and scratching, a solid, m. p. 41—44° (7·5 g., 77%); after several crystallisations from light petroleum (b. p. 40—60°), green crystals, m. p. 48° (*ca.* 45—50%) of N-*methyl*-p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline* were obtained (Found: C, 73·2; H, 9·7; N, 10·8. $C_{14}H_{26}ON_2$ requires C, 73·3; H, 9·9; N, 10·7%).

Other attempted nitrosation procedures gave incomplete reaction. Rapidity of working-up of the nitrosated material is essential.

The yellow *hydrochloride* was obtained from light petroleum (b. p. 60—80°) solution; purified from alcohol–ether, it had m. p. 134° (decomp.) (Found: C, 64·0; H, 9·0; N, 9·6; Cl, 12·4. $C_{14}H_{27}ON_2Cl$ requires C, 64·3; H, 9·0; N, 9·4; Cl, 11·9%). On reduction with zinc dust in aqueous hydrochloric acid (1 : 1) it gave the crude diamine as a violet oil which with 1-chloro-2 : 4-dinitrobenzene in very concentrated alcoholic solution gave, after recrystallisation from alcohol, 4-(N-*methyl*-N-3 : 5 : 5-*trimethylhexylamino*)-2′ : 4′-*dinitrodiphenylamine hydrochloride*, m. p. 205°, which darkened in air (Found: C, 58·7; H, 6·9; N, 12·7; Cl, 7·9. $C_{22}H_{31}O_4N_4Cl$ requires C, 58·6; H, 6·9; N, 12·4; Cl, 7·9%). With aqueous potassium carbonate this gave, after crystallisation of the products from ethanol and then from light petroleum (b. p. 60—80°), reddish-brown 4-(N-*methyl*-N-3 : 5 : 5-*trimethylhexylamino*)-2′ : 4′-*dinitrodiphenylamine*, m. p. 65·5° (Found: C, 63·8; H, 7·4; N, 13·5. $C_{22}H_{30}O_4N_4$ requires C, 63·8; H, 7·3; N, 13·5%).

N-*Ethyl*-N-3 : 5 : 5-*trimethylhexylaniline*.—This was prepared in the same way as the corresponding *N*-methyl compound [*N*-ethylaniline (48·4 g.) replacing methylaniline], in 85% yield. The *base* was straw-coloured and had b. p. 140°/2·5 mm., n_D^{20} 1·5091 (Found: C, 82·1; H, 11·9; N, 5·7. $C_{17}H_{29}N$ requires C, 82·5; H, 11·7; N, 5·7%). The addition compound with picrolonic acid was unstable in ether.

N-*Ethyl*-p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline*.—The base (10 g.) in acetic acid (60 c.c.) and concentrated hydrochloric acid (12·5 c.c.) was nitrosated with stirring at 0° with sodium nitrite (3·6 g., *ca.* 30% excess) in water within 5 min. After a further 5 minutes' stirring the solution was made alkaline with potassium carbonate and extracted with light petroleum (b. p. 40—60°), and the washed (water) and dried ($MgSO_4$) extract was filtered and evaporated. The residual dark green oil did not solidify. In light petroleum (b. p. 60—80°) it gave N-*ethyl*-p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline hydrochloride* (7·4 g., 59%) as a flocculent, yellow precipitate (crude m. p. 122°). Crystallisation from ethanol–ether gave yellow crystals, m. p. 129° (decomp.) (Found: C, 65·4; H, 9·3; N, 8·7; Cl, 11·4. $C_{17}H_{29}ON_2Cl$ requires C, 65·2; H, 9·2; N, 9·0; Cl, 11·4%). Aqueous sodium hydroxide liberated the base which was extracted with light petroleum (b. p. 40—60°); the washed (water), dried ($MgSO_4$), and filtered extract was evaporated, giving N-*ethyl*-p-*nitroso*-N-3 : 5 : 5-*trimethylhexylaniline* as a green oil (Found: C, 74·1; H, 10·1; N, 10·3. $C_{17}H_{28}ON_2$ requires C, 74·0; H, 10·1; N, 10·1%). Reduction of the hydrochloride (3 g.) with zinc dust in aqueous-alcoholic hydrochloric acid gave the diamine as a violet oil (2 g.). Condensation with 1-chloro-2 : 4-dinitrobenzene in alcohol, treatment of the solid obtained with aqueous 1% sodium hydroxide, extraction with light petroleum (b. p. 60—80°), and concentration of the dried extract gave 4-(N-*ethyl*-N-3 : 5 : 5-*trimethylhexylamino*)-2′ : 4′-*dinitrodiphenylamine* as brick-red crystals, which, after further purification from light petroleum (b. p. 60—80°), melted at 80·5° (Found: C, 64·2; H, 7·3; N, 13·3. $C_{23}H_{32}O_4N_4$ requires C, 64·5; H, 7·5; N, 13·1%).

RESEARCH DEPARTMENT, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
BILLINGHAM DIVISION, BILLINGHAM, CO. DURHAM. [*Received, January 25th*, 1955.]

Calculated Bond Lengths in Some Cyclic Compounds. Part I. Methods of Calculation.

By T. H. Goodwin and V. Vand.

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A description is given of new methods of expanding secular determinants and solving the resulting equation for the energy levels in molecular-orbital calculations of bond orders as well as for evaluating the secular coefficients (c_r^i). A new curve for correlating bond order and bond length is also proposed.

A refinement of the simplest valency bond counting method is described and a correlation curve for use with it is suggested.

Determinations of the crystal structures of condensed ring compounds made in these laboratories under the direction of Professor J. M. Robertson have established the bond lengths in many such substances with considerable or very great accuracy. Complementary to these practical investigations have been wave-mechanical studies of the theoretical values to be expected for the bond orders and hence for the bond lengths in some of the compounds examined by *X*-rays [see, for example, Coulson, Daudel, and Robertson (*Proc. Roy. Soc.*, 1951, *A*, **207**, 306) who discuss the results for naphthalene, anthracene, coronene, ovalene, pyrene, etc., and Coulson (*ibid.*, p. 91)]. In the present series of papers calculations are presented on a number of substances. For some of them the interatomic distances have already been measured and so can profitably be compared with the calculations. For others the calculations have been made in the hope of using the resulting bond lengths in setting up molecular models for use in refining the crystal structures. This first Part describes what are believed to be new methods of carrying out the calculations for very large molecules, of which benzanthrone, to which the technique was first applied, may be taken as typical.

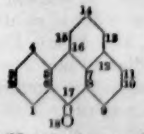
Molecular-orbital Calculations

Benzanthrone (I), $C_{17}H_{10}O$, has 18 π-electrons, and the 18 secular equations

$$\sum_r c_r^i(H_{rs} - ES_{rs}) = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

were set up in the usual way.

As the determinant Δ formed by the coefficients of the c_r^i is of the eighteenth order and has no simplifying symmetry, inclusion of overlap would greatly increase the labour of evaluating



(I) (Numbering used for mathematical calculations for benzanthrone.)

$$\begin{vmatrix} x & 1 & 0 & 0 & 0 \\ 1 & x & 1 & 0 & 0 \\ 0 & 1 & x & 1 & 0 \\ 0 & 0 & 1 & x & 1 \\ 0 & 0 & 0 & 1 & x \end{vmatrix}$$

(*A*)

the coefficients c_r^i of the normalised atomic orbitals ϕ_r, making up the molecular orbitals $\psi_i = \sum_r c_r^i \phi_r$ and so it was decided that the overlap integrals $S_{rs} = \int \phi_r \phi_s d\tau$ should be placed equal to zero, except for $S_{rr} = 1$. The following further simplifications were adopted: for all carbon atoms the Coulomb integral $H_{rr} = \alpha$; for the oxygen atom $H_{18,18} = \alpha + \beta$; resonance integrals H_{rs} between adjacent carbon atoms = β, between adjacent carbon and oxygen atoms = 2β, between other atoms = 0. The molecular orbital energy levels E_i were obtained in terms of β by writing $x_i = (\alpha - E_i)/\beta$ and solving the equation $\Delta = 0$.

This and subsequent stages of the work are very conveniently carried out by use of

determinants of the variety known as continuants of which P_5, in inset (*A*), is an example. The following are some properties of continuants which are useful for the present purpose :

$$P_n = xP_{n-1} - P_{n-2} \text{ with } P_0 = 1;\ P_1 = x;\ P_2 = x^2 - 1, \text{ etc.} \quad . \quad . \quad (2)$$

$$P_n.P_m = P_{n+m} + P_{n+m-2} + P_{n+m-4} + \ldots\ldots + P_{n-m+2} + P_{n-m} \quad . \quad . \quad (3)$$

where $n > m$.

$$P_n^2 = P_{2n} + P_{2n-2} + \ldots\ldots + P_2 + P_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$dP_n/dx = nP_{n-1} + (n-2)P_{n-3} + (n-4)P_{n-5} + \ldots\ldots + 2P_1 \text{ or } P_0 \quad . \quad (5)$$

according as n is even or odd. Continuants are, in fact, the Tschebysheff polynomials

$$P_n = x^n - \frac{n-1}{1}x^{n-2} + \frac{(n-2)(n-3)}{1.2}x^{n-4} \ldots\ldots \quad . \quad . \quad . \quad . \quad (6)$$

and may also be written as

$$P_n = 2[\cos n\theta + \cos(n-2)\theta + \cos(n-4)\theta + \ldots\ldots (\cos\theta \text{ or } \tfrac{1}{2})] \quad . \quad . \quad (7)$$

according as n is odd or even. This transformation depends on the substitution $x = 2\cos\theta$ and means that a sum of continuants $aP_n + bP_m + \ldots\ldots$ can readily be expressed as a Fourier series and so evaluated very rapidly by any of the strip, stencil, or other methods (*e.g.*, Lipson and Beevers, *Proc. Phys. Soc.*, **1936**, **48**, 772; *Acta Cryst.*, **1952**, **5**, 670; Robertson, *Phil. Mag.*, **1936**, **21**, 176; *J. Sci. Instr.*, **1948**, **25**, 28) used by crystallographers and others for computing Fourier syntheses, provided the argument x ($\cos\theta$) lies between ± 2 (± 1).

The expansion of the determinant Δ is, then, carried out by expressing it as a sum of continuants since it is, in fact, a continuant with various " decorations," *viz.*, the terms not on the leading and immediately adjacent diagonals and such of these terms as are not x (leading diagonals) or 1 (adjacent diagonals). If there are decorations, b, in the original determinant at (pq) and (qp), *i.e.*, at the intersections of column p with row q and of column q with row p, then one of these (say that at pq) may be removed by writing

$$\Delta = \Delta'_1 + (-1)^{p+q} b\Delta'_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where Δ'_1 is derived from Δ by suppressing the b at (pq) and Δ'_2 is the minor of the b at (pq) in Δ. To remove both b's simultaneously write

$$\Delta = \Delta_1 + 2(-1)^{p+q} b\Delta_2 - b^2\Delta_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where Δ_1 is derived from Δ by suppressing both b's, Δ_2 is the minor of the b at (pq) in Δ but with the b at (qp) also suppressed, and Δ_3 is the " double minor " of the b's, *i.e.*, columns p and q and rows p and q of Δ are all suppressed. Note that if Δ is of order n, so are Δ_1 and Δ'_1; Δ_2 and Δ'_2 are of order $n-1$, and Δ_3 is of order $n-2$. Also Δ_1 and Δ_3 are, like Δ, axially symmetrical but Δ_2 is not. Δ_2 is, however, often found to be immediately factorised and is frequently zero. If not zero it or its factors may be treated by (8) to break it up further; factors are multiplied out by means of (3). Δ_1 and Δ_3 are of course treated as in (9). This process is repeated until all " decorations " have been removed. Thus, in quite a short time the eighteenth order determinant of benzanthrone was expanded to

$$P_{18} + P_{17} - 7P_{16} - 4P_{15} + 8P_{14} - P_{12} - 5P_{11} + 29P_{10} + 10P_9 - 13P_8 + \\ + 5P_7 + 6P_6 + 17P_5 - 52P_4 + 7P_3 - 9P_2 + 8P_1 - 36P_0 = 0 \quad . \quad (10)$$

a simpler form than the equivalent

$$x^{18} + x^{17} - 24x^{16} - 20x^{15} + 233x^{14} + 161x^{13} - 1197x^{12} - 681x^{11} + \\ + 3571x^{10} + 1655x^9 - 6391x^8 - 2367x^7 + 6831x^6 + 1947x^5 - 4170x^4 + \\ - 842x^3 + 1290x^2 + 146x - 144 = 0 \quad . \quad (11)$$

An important feature of all work of this kind is the application of checks on accuracy. When

the method of continuants is used these are particularly simple, as the following table of values of P_n for $x = 0, 1, 2$ shows :

x	n: 0	1	2	3	4	5	6	7	8
0	1	0	−1	0	1	0	−1	0	1
1	1	1	0	−1	−1	0	1	1	0
2	1	2	3	4	5	6	7	8	9

Also $P_{2n}(x) = +P_{2n}(-x)$, and $P_{2n+1}(x) = -P_{2n+1}(-x)$

Expansion (10) having been reached, inspection shows that $(x - 1)$ and $(x + 1)$ and therefore $(x^2 - 1)$ are factors of the left-hand side. Since $P_2 = x^2 - 1$ these factors are removed by division, using (3). Actually P_2 can also be removed again and finally $(x + 1)$ which is written as $P_1 + P_0$.

The remaining thirteenth-order equation, R, is then solved by writing it as a Fourier series by use of (7) and summing and plotting it between $\theta = 0$ and π ($x = \pm 2$). The nodes of this curve are at those roots of R which lie between $x = \pm 2$ but will only be given approximately by this method. To obtain them more accurately an iterative process is used. The values of P_n for $0 < n < 13$ were calculated by (2) and checked by (6), using Horner's method. These results are then used to evaluate accurately R and its derivatives R' and R'' at the approximate values of the roots; application of Taylor's theorem in the form

$$R(x + h) = R(x) + \frac{h}{1!}R'(x) + \frac{h^2}{2!}R''(x) = 0 \quad . \quad . \quad . \quad . \quad (12)$$

gives, to this approximation, the increment h by which x may be increased to get a better value of the root for further iteration.

Since the parameter β in units of which x is obtained is negative, only the negative roots of R are required in studying the ground state of the molecule. The rest may, of course, be obtained to use as a check on their correct extraction. To determine the roots lying outside the limits $x = \pm 2$ the accurate factors were removed from R and the residue, a function containing P_5, was examined by a combination of guess work, Taylor's theorem, and experience. The last shows that for hydrocarbons nearly all the roots are between $+2$ and -2 and so the Fourier technique described above is very helpful. It becomes less useful as the compound contains more and more heteroatoms.

The c_r^i are also easily evaluated by means of continuants as may readily be illustrated by means of the simple example of benzene, the secular equations of which are those indexed a to f below.

	c_1	c_2	c_3	c_4	c_5	c_6		
a	x	1	0	0	0	1	$= 0$	$a - xb$ gives g
b	1	x	1	0	0	0	$= 0$	$b - xc$ gives i
c	0	1	x	1	0	0	$= 0$	$c - xd$ gives l
d	0	0	1	x	1	0	$= 0$	
e	0	0	0	1	x	1	$= 0$	
f	1	0	0	0	1	x	$= 0$	$f - b$ gives k
g	0	$-P_2$	$-P_1$	0	0	1	$= 0$	$g + P_2c$ gives j
h	0	$-P_1$	$-P_0$	0	P_0	P_1	$= 0$	$h + P_1c$ gives k
i	1	0	$-P_2$	$-P_1$	0	0	$= 0$	$i + P_2d$ gives m
j	0	0	P_2	P_1	0	P_0	$= 0$	
k	0	0	P_2	P_1	P_0	P_1	$= 0$	
l	0	1	0	$-P_2$	$-P_1$	0	$= 0$	
m	1	0	0	P_2	P_2	0	$= 0$	

The object is to write a simple expression for each coefficient in terms of as few others as possible and the method is sufficiently illustrated by the notes given beside the equations. The final set of equations is given as p to u from which it is seen that they are in fact relatively simple to write down and a simple equation gives c_5 in terms of c_6 and the rest simiarly. Incidentally the

	c_1	c_2	c_3	c_4	c_5	c_6	
p	0	0	0	1	P_1	1	$= 0$
q	0	0	1	0	$-P_2$	$-P_1$	$= 0$
r	0	1	0	0	P_3	P_2	$= 0$
s	1	0	0	0	$-P_4$	$-P_3$	$= 0$
t	0	0	0	0	P_5	$1 + P_4$	$= 0$
u	0	0	0	0	$1 + P_4$	$P_3 + P_1$	$= 0$

determinant of the coefficients of c_5 and c_6 in t and u is equivalent to the secular determinant Δ. The larger set of equations for benzanthrone is given in (13) in which

$A = P_6 - P_4 - 1$; $B = -(P_3 + P_1)$; $C = P_6 + P_4 + 1$; $D = P_7 + P_3$; $E = P_7 + 2P_3 + P_1$; $F = -P_7 + P_5 + P_3 + P_1$; $G = P_4 + 2P_2$; $H = -P_6 + P_4 + P_1$. Hence, from equations *f*, *h*, *i*, *q*, *r* and a Table of P_n for $x =$ the root, the values of c_5, c_6, c_7, c_{17}, c_{18} for each energy

	c_1	c_2	c_3	c_4	c_5	c_6	c_7	c_8	c_9	c_{10}	c_{11}	c_{12}	c_{13}	c_{14}	c_{15}	c_{16}	c_{17}	c_{18}	
(*a*)	0	0	0	0	P_6	$P_4 + 1$	0	0	0	0	0	0	0	0	0	P_4	0	0	$= 0$
(*b*)	1	0	0	0	$-P_4$	$-P_2$	0	0	0	0	0	0	0	0	0	$-P_2$	0	0	$= 0$
(*c*)	0	1	0	0	P_2	P_0	0	0	0	0	0	0	0	0	0	P_0	0	0	$= 0$
(*d*)	0	0	1	0	$-P_2$	$-P_1$	0	0	0	0	0	0	0	0	0	$-P_1$	0	0	$= 0$
(*e*)	0	0	0	1	P_1	1	0	0	0	0	0	0	0	0	0	1	0	0	$= 0$
(*f*)	0	0	0	0	$P_4 + 1$	$P_2 + P_1$	0	0	0	0	0	0	0	0	0	P_2	1	0	$= 0$
(*g*)	0	0	0	0	0	0	P_1	1	0	0	0	1	0	0	0	1	0	0	$= 0$
(*h*)	0	0	0	0	A	B	C	0	0	0	0	0	0	0	0	$P_5 - P_3$	0	0	$= 0$
(*i*)	0	0	0	0	D	0	E	0	0	0	0	0	0	0	0	C	0	0	$= 0$
(*j*)	0	0	0	0	P_6	0	$P_5 + P_3$	0	1	0	0	0	0	0	0	P_7	0	0	$= 0$
(*k*)	0	0	0	0	$-P_4$	0	$-P_3 - P_1$	0	0	1	0	0	0	0	0	$-P_4$	0	0	$= 0$
(*l*)	0	0	0	0	P_4	0	$P_4 + 1$	0	0	0	1	0	0	0	0	P_5	0	0	$= 0$
(*m*)	0	0	0	0	$-P_2$	0	$-P_2$	0	0	0	0	1	0	0	0	$-P_4$	0	0	$= 0$
(*n*)	0	0	0	0	P_2	0	P_2	0	0	0	0	0	1	0	0	P_3	0	0	$= 0$
(*o*)	0	0	0	0	$-P_1$	0	$-P_1$	0	0	0	0	0	0	1	0	$-P_3$	0	0	$= 0$
(*p*)	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1	P_1	0	0	$= 0$
(*q*)	0	0	0	0	F	G	$-D$	0	0	0	0	0	0	0	0	H	0	-2	$= 0$
(*r*)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	$P_1 + 1$	$= 0$

(13)

level can be expressed in terms of c_{18}. From these the rest are readily obtained also in terms of c_{18} and then evaluated by use of the normality condition $\sum_r (c_r^i)^2 = 1$ and the orthogonality condition $\sum_r (c_r^i c_r^j) = 0$. The electron distribution q and mobile bond orders p can then be deduced from

$$q_r = \sum_i n(c_r^i)^2$$

and

$$p_{rs} = \sum_i n c_r^i c_s^i$$

summation being over all the occupied energy levels, usually with $n = 2$ electrons in each.

To determine the bond lengths L_1 reference was made to a curve drawn through the following points:

		Mobile bond order	Bond length
D	Diamond corrected to sp^2 hybridisation	0	1·50
G	Graphite	0·525	1·421
B	Benzene	0·667	1·39
E	Ethylene	1·00	1·34

This curve (Fig. 1) is almost rectilinear and so interpolation is simple. The arguments for the diamond point are given by Coulson (Victor Henri Memorial Volume, "Contribution à l'Étude de la Structure Molèculaire," Desoer, Liège, 1948); the others are long established. However, Cox and Smith's work (*Nature*, 1954, **173**, 75) suggests a benzene point of (0·667, 1·378) with an uncertainty of 0·003 Å in the bond length. This measurement, made on crystals at −3°, is significantly different from Stoicheff's value 1·396—1·401 Å (*J. Chem. Phys.*, 1953, **21**, 1410) derived from Raman spectrum data on the vapour at 61°. Even after allowance for the difference of state this discrepancy is so great that temporary use of the old intermediate value of 1·39 Å seems to be the correct course.

Alternatively, conversion of bond orders into bond lengths might be effected by use of Coulson's "best correlation curve" (*Proc. Roy. Soc.*, 1951, *A*, **207**, 95, Fig. 2b) which is derived from the generally very accurate measurement of thirty-six distinct bond lengths in nine hydrocarbons, the bond orders being obtained by the molecular-orbital approximation. This curve (Fig. 1) passes through the points (measured from the figure) (0·466, 1·46); (0·5, 1·443); (0·6, 1·406); (0·7, 1·378); (0·8, 1·361); (0·9, 1·351); (1·0, 1·34). Unfortunately the extrapolation of this to mobile bond orders lower than 0·4, such as are obtained for some of the compounds to be discussed, is not practicable as it would lead to a length of *ca.* 1·495 for order 0·4 and *ca.* 1·58 for order 0·3. However, by using the same parameters as for benzanthrone, it is found that in benzoquinone the bonds adjacent to the keto-group have mobile orders of 0·310 and, according to the measurement reported by Robertson (*Proc. Roy. Soc.*, 1935, *A*, **150**, 106), a length of 1·50. This value, obtained twenty years ago, is not, of course, known with the precision of modern measurements. It is, therefore, being measured again in this Department

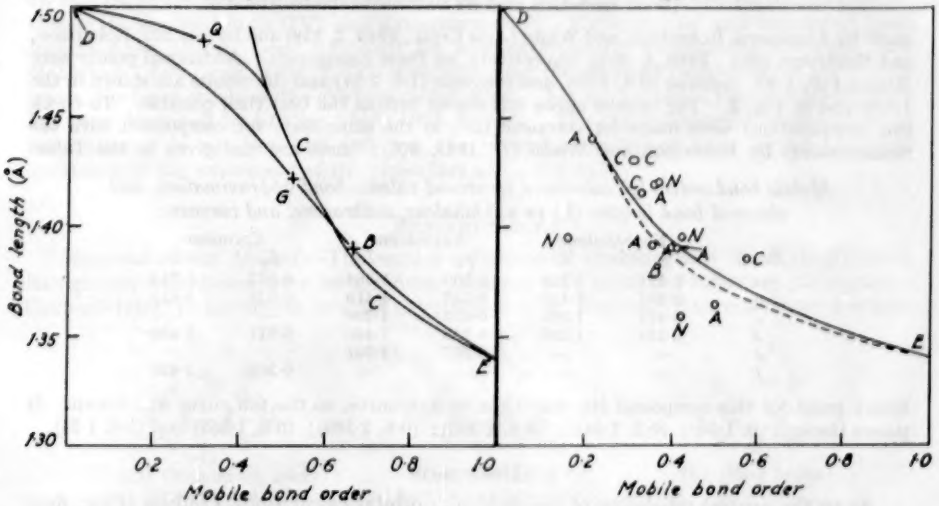
but, in the meantime, we may recognise that it is reliable to within a few hundreds of an Ångström. In particular if we take its length to be 1·485 Å the Coulson curve may be extrapolated through (0·310, 1·485) to (0, 1·50) to provide a graph for correlations at low order to within a few hundredths of an Angstrom unit.

Throughout this series of papers, therefore, bond lengths will be described as L_1 when derived from the curve *DGBE* and as L_2 when derived from the Coulson curve extended through benzoquinone *Q* to diamond. The latter curve will be called *DQCE*. This extrapolation is rather arbitrary but fortunately orders less than 0·5 are seldom required and unfortunately there are no other points available. Nowhere do these two curves differ by more than 0·026 Å and in the most important region (orders greater than 0·55) by more than 0·008 Å.

It is of interest that graphite (0·525, 1·421) lies below this curve by about 0·01 Å and the benzene point *B* above it by 0·005 Å while the newer crystallographic benzene point is below it by 0·008 Å. It is also clear that benzene and graphite are unsatisfactory standards for correlating orders and lengths in polycyclic compounds since graphite, considered as an infinite sheet has no " edge effects," *i.e.*, no carbon atoms linked to only two others, while benzene is all

FIG. 1. *Correlation curves for molecular-orbital method.*

FIG. 2. *Correlation curves for second valence-bond approximation.*



edge effects, *i.e.*, has no carbon atoms linked to three others. It amounts to the same thing to say that the approximations used in calculating bond orders are, in fact, too naïve to cover all types of compound adequately.

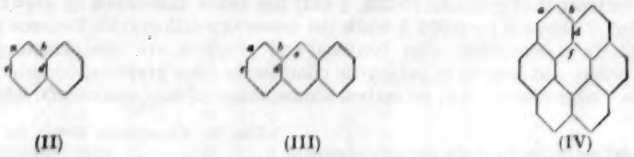
The correlation of orders and lengths for C=O is much less satisfactory, as Cox and Jeffrey have pointed out (*ibid.*, 1951, *A*, **207**, 110). For the compounds discussed in this paper a linear interpolation has been made between 1·185 Å for a double bond and 1·437 Å for a single bond on the basis of data given by these authors, but with the note that the calculated bond order of a pure double bond is 0·895 Å as shown by Coulson (*Trans. Faraday Soc.*, 1946, **42**, 106). As the orders calculated are all greater than 0·85 the uncertainties are not very serious. For C–N bonds Cox and Jeffrey's linear correlation curve (*loc. cit.*, p. 115) was used.

VALENCE-BOND CALCULATIONS

Calculations by the valence-bond method have been made by the two simplest approximations. In the first of these (Pauling, Brockway, and Beach, *J. Amer. Chem. Soc.*, 1935, **57**, 2705) only unexcited canonical structures were included. It follows that bonds **5–16**, **6–17**, and **8–17** (see I) of benzanthrone are necessarily single bonds so that ring **1,2,3,4,5,6** can have only the two canonical structures of benzene while the double ring **7,8,9,10,11,12,13,14,15,16** must have the three of naphthalene. By counting *N*, the number of times a given bond is double in the total of six structures, the bond order *p* is obtained as $N/6$ whence Pauling's correlation curve

(" Nature of the Chemical Bond," Cornell Univ. Press, New York, 1945, p. 174) modified for the sp^3 diamond leads at once to the bond lengths L_3.

In the second valence-bond approximation unexcited and first excited structures, *i.e.*, structures with not more than one long bond, were included, with the proviso that no long bond should traverse more than two rings. There are fifty-four such structures, including the six referred to in the previous paragraph, and by the method indicated there the orders are readily obtained, equal weights being given to unexcited and excited structures. The authors know of no established order–length curves for use with such calculations and it is difficult to set up one using graphite as one of the standards. To get over this difficulty the corresponding calculations were made on naphthalene (II) and anthracene (III) for use with the measurements



(II) (III) (IV)

(Bond symbolism used for mathematical calculations.)

made by Abrahams, Robertson, and White (*Acta Cryst.*, 1949, **2**, 238) and by Sinclair, Robertson, and Mathieson (*ibid.*, 1950, **3**, 251), respectively, on these compounds. Additional points were diamond (0, 1·50), benzene (0·4, 1·39), and ethylene (1·0, 1·34) and the results are shown in the Table and in Fig. 2. The broken curve was drawn first as the best then possible. To check this computations were made for coronene (IV) in the same way, for comparison with the measurements by Robertson and White (*J.*, 1945, 607); these are also given in the Table.

Mobile bond orders (p) *calculated by second valence-bond approximation, and observed bond lengths* (L) *in naphthalene, anthracene, and coronene.*

	Naphthalene		Anthracene		Coronene	
Bond	p_4	L	p_4	L	p_4	L
a	0·421	1·359	0·500	1·364	0·573	1·385
b	0·367	1·420	0·357	1·419	0·328	1·415
c	0·421	1·395	0·405	1·390	—	—
d	0·158	1·395	0·215	1·440	0·311	1·430
e	—	—	0·357	1·391	—	—
f	—	—	—	—	0·305	1·430

Every point for this compound lay above the broken curve, so the full curve was drawn. It passes through (0, 1·50); (0·2, 1·445); (0·4, 1·393); (0·6, 1·369); (0·8, 1·353) and (1·0, 1·34).

Discussion

As to the general reliability of the molecular-orbital calculations, Coulson (*Proc. Roy. Soc.*, 1951, *A*, **207**, 91) and Coulson, Daudel, and Robertson (*loc cit.*) show that for aromatic hydrocarbons both molecular-orbital calculations and good *X*-ray work permit the estimation of bond lengths to about 0·02 Å, and that the results obtained by the two methods agree within the same limits. Coulson (*loc. cit.*) also indicates that for hetero-molecules the agreement is not generally closer than ±0·05 Å, but this will clearly depend on the perturbations caused by the hetero-atoms. Thus benzanthrone, considered in Part II, contains one hetero-atom out of eighteen supplying π-electrons. It is thus essentially a large aromatic hydrocarbon with a local perturbation. The molecular-orbital calculations ought, therefore, to be accurate to ±0·03 Å except, perhaps, for the C–C bonds attached to the keto-carbon atom, for which the order–length curve is less reliable. With more hetero-atoms or fewer carbon atoms the uncertainty is likely to be greater and so will be discussed for each compound in turn (see following paper).

The authors gratefully acknowledge the helpful interest of Professor J. M. Robertson, F.R.S., and Professor C. A. Coulson, F.R.S., in this work.

Chemistry Department, University of Glasgow.
(Present address of V. V.: Pennsylvania State University,
State College, Penn., U.S.A.) [*Received, November 22nd*, 1954.]

Calculated Bond Lengths in Some Cyclic Compounds. Part II. Benzanthrone, Acedianthrone, and Flavanthrone.*

By T. H. Goodwin.

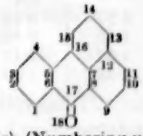
[Reprint Order No. 5901.]

With the help of the methods developed in Part I the energy levels, bond orders, and bond lengths in benzanthrone, acedianthrone, and flavanthrone have been deduced by the molecular-orbital method. Bond orders and bond lengths in benzanthrone have also been derived by the two simple valence-bond approximations of the previous paper. For the second and the third compound the observed and the calculated interatomic distances agree very satisfactorily within the experimental uncertainty except for a very few bonds. The crystallographic examination of benzanthrone is not yet complete but the present calculations have been used in suggesting refinements.

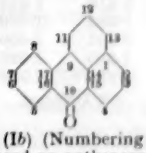
In this paper the methods of calculation developed in Part I have been applied to benzanthrone (I), acedianthrone (IV), and flavanthrone (V). Experimental and calculated bond lengths have already been compared for acedianthrone by Friedlander, Goodwin, and Robertson (*Acta Cryst.*, 1954, **7**, 127) without noting the assumed parameters or the energy levels, the bond orders or the electron distribution. For flavanthrone the crystal structure has been described by Stadler (*ibid.*, 1953, **6**, 540). The crystallographic examination of benzanthrone is not yet complete but the present calculations have already been of assistance in the refinement of the projection along one axis.

Benzanthrone

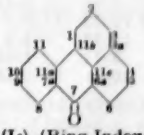
Molecular-orbital Method.—The secular equations of benzanthrone (I), $C_{17}H_{10}O$, with its eighteen π-electrons, were set up in the ordinary way using the following parameters: Coulomb integrals for carbon $= \alpha$, for oxygen $= \alpha + \beta$; exchange integrals between neighbouring carbon atoms $= \beta$, between neighbouring C and O atoms $= 2\beta$, between all other pairs of atoms $= 0$; overlap integrals $= 0$. They lead to an eighteenth-order secular determinant which cannot readily be factorised but which, when treated by the methods indicated in Part I, yields first the energy levels E_i listed in Table 1, then the electron distribution (q) noted in Table 2, and finally the bond orders (p_{12}) and the bond lengths L_1 and L_2 of Table 3. The values L_1 and L_2 were derived from the correlation curves *DGBE* and *DQCE* forming Fig. 1 of Part I.



(Ia) (Numbering used for mathematical calculations.)



(Ib) (Numbering based on anthracene)



(Ic) (Ring Index No. 2812.)

Table 1. *Molecular-orbital energy levels for benzanthrone in order of increasing energy.*

i	E_i	i	E_i	i	E_i	i	E_i
1	$\alpha + 2{\cdot}9928\beta$	6	$\alpha + \beta$	11	$\alpha - 0{\cdot}8693\beta$	15	$\alpha - 1{\cdot}5718\beta$
2	$\alpha + 2{\cdot}3125\beta$	7	$\alpha + \beta$	12	$\alpha - \beta$	16	$\alpha - 1{\cdot}9654\beta$
3	$\alpha + 2{\cdot}0439\beta$	8	$\alpha + \beta$	13	$\alpha - \beta$	17	$\alpha - 2{\cdot}1270\beta$
4	$\alpha + 1{\cdot}6212\beta$	9	$\alpha + 0{\cdot}5534\beta$	14	$\alpha - 1{\cdot}3446\beta$	18	$\alpha - 2{\cdot}6523\beta$
5	$\alpha + 1{\cdot}40349\beta$	10	$\alpha - 0{\cdot}3968\beta$				

Valence-bond Methods.—Again, by using techniques described in Part I, the bond orders

* Part I, preceding paper.

p_3 and p_4 were evaluated by valence-bond approximations and the corresponding bond lengths L_3 and L_4 were obtained from the curves of Fig. 2 of that reference. These results have also been included in Table 3.

TABLE 2. *Electron distribution* (q) *in benzanthrone (molecular-orbital method).*

Atom, numbered according to :				Atom, numbered according to :				Atom, numbered according to :			
(I*a*)	(I*b*)	(I*c*)	*q*	(I*a*)	(I*b*)	(I*c*)	*q*	(I*a*)	(I*b*)	(I*c*)	*q*
1	5	8	0·973	7	14	11*c*	0·991	13	13	3	0·978
2	6	9	1·002	8	15	6*a*	1·032	14	12	2	0·998
3	7	10	0·979	9	4	6	0·964	15	11	1	0·967
4	8	11	0·992	10	3	5	1·010	16	9	11*b*	0·986
5	17	11*a*	0·960	11	2	4	0·967	17	10	7	0·830
6	16	7*a*	1·024	12	1	3*a*	1·001	18*	O	O	1·345

* Oxygen.

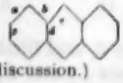
TABLE 3. *Mobile bond orders* (p) *and bond lengths* (L) *in benzanthrone.*

Bond, numbered according to :			Molecular-orbital method			Valence-bond methods			
						Method 1		Method 2	
(I*a*)	(I*b*)	(I*c*)	p_{12}	L_1	L_2	p_3	L_3	p_4	L_4
1–2	5–6	8–9	0·668	1·390	1·386			0·50	1·379
1–6	5–16	7*a*–8	0·638	1·397	1·394			0·44	1·387
2–3	6–7	9–10	0·649	1·394	1·391			0·43	1·389
3–4	7–8	10–11	0·673	1·389	1·384	0·50	1·39	0·52	1·377
4–5	8–17	11–11*a*	0·600	1·404	1·406			0·41	1·391
5–6	16–17	7*a*–11*a*	0·573	1·411	1·416			0·35	1·403
5–16	9–17	11*a*–11*b*	0·372	1·454	1·479			0·13	1·468
6–17	10–16	7–7*a*	0·321	1·463	1·484	0	1·50	0	1·50
7–8	14–15	6*a*–11*c*	0·561	1·413	1·420			0·39	1·395
7–12	1–14	3*a*–11*c*	0·533	1·420	1·431	0·33	1·42	0·17	1·455
7–16	9–14	11*b*–11*c*	0·507	1·426	1·440			0·31	1·413
8–9	4–15	6–6*a*	0·684	1·387	1·381	0·67	1·37	0·46	1·384
8–17	10–15	6*a*–7	0·303	1·466	1·486	0	1·50	0	1·50
9–10	3–4	5–6	0·627	1·399	1·397	0·33	1·42	0·41	1·391
10–11	2–3	4–5	0·723	1·379	1·374	0·67	1·37	0·48	1·382
11–12	1–2	3*a*–4	0·558	1·414	1·421	0·33	1·42	0·35	1·403
12–13	1–13	3–3*a*	0·551	1·416	1·423			0·41	1·391
13–14	12–13	2–3	0·709	1·382	1·376	0·67	1·37	0·43	1·389
14–15	11–12	1–2	0·616	1·401	1·400	0·33	1·42	0·46	1·384
15–16	9–11	1–11*b*	0·642	1·395	1·392	0·67	1·37	0·41	1·391
17–18*	10–O	7–O	*0·884*	*1·188*	*1·188*	*1·00*	*1·185*	*1·00*	*1·185*

* Oxygen.

Discussion.—The discussion of accuracies in the preceding paper (p. 1688) shows that the molecular-orbital calculation of bond length ought to be accurate to ±0·03 Å, except perhaps for the bonds attached to carbonyl carbon. Three decimal places are given for bond orders and bond lengths simply to permit their more accurate use in subsequent work.

For benzanthrone the results obtained by the molecular-orbital method (either curve : the figures quoted below refer to *DQCE*) may be regarded as satisfactory pending completion of *X*-ray measurements. The bonds 5–16, 6–17, and 8–17, which are all single bonds on the first valence-bond approximation, are found to be 1·479, 1·484, and 1·486 Å respectively. These are greater than the characteristic length of *ca.* 1·39 Å found in aromatic compounds and shorter than pure single bonds, but virtually identical with the 1–2 bond in *p*-benzoquinone (see Part I, p. 1686). These results therefore represent an acceptable compromise between the wholly aromatic character of the compound and the general importance of structures of the Kekulé type in explaining the properties of condensed ring compounds.

(II)  (III)

(Bond symbolism used in the discussion.)

Bonds 5–6, 7–8, 7–12, and 7–16, the internal bonds, vary from 1·416 to 1·440 Å, being of the same order as the internal bonds *d* of naphthalene (II) and anthracene (III). The remaining twelve peripheral bonds vary from 1·374 to 1·423 Å though only three exceed

1·400 Å; there is no marked classification into links of the types *a*, *b*, and *c* of naphthalene and anthracene, which show significant differences in the Table in Part I. It is true that there is an alternation in the lengths of the peripheral bonds in the chains between atoms 5 and 6, 8 and 12, and 12 and 16, but the differences are very small and of doubtful significance in view of the coarseness of the fundamental approximations: further, two "long" bonds meet at atom 12.

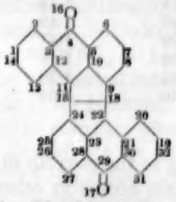
There is a marked alternation of electron density from atom 1 to atom 18 (Table 2), thus illustrating the law of alternating polarity pointed out by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **192**, 16) for hetero-molecules; the sequence of numbering the atoms for the calculations emphasises the alternation. The chemistry, however, does not point to any marked concentration or deficiency of electrons anywhere in the molecule though it seems that anionic and cationic reagents are respectively rather more active at atoms 9 and 13; these, however, both appear, from the calculations, to be electron-deficient atoms.

Of the two valence-bond approximations the first is particularly inadequate and the second, though a marked improvement, still suffers from the deficiencies inherent in the method. It was attempted solely to try to circumvent the difficulty that the first, although generally leading to reasonable predictions of order and length, requires that in benzanthrone (and all aromatic quinones) some of the bonds shall be regarded as pure single bonds. It did not seem worth while to attempt the more rigorous full application of the valence-bond method (*e.g.*, Wheland and Pauling, *J. Chem. Phys.*, 1933, **1**, 362; Sherman, *ibid.*, 1934, **2**, 488) to this compound.

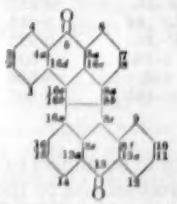
The crystallographic examination of benzanthrone has proved unusually difficult but is now well advanced. The calculations given above have been used in carrying out the refinement of the first zone as follows. At a certain stage the atoms were located approximately. There are three characteristic bond directions at 120° to each other in the molecule. The ratios of the projected to the predicted bond lengths in each of these directions were calculated. Three atoms (numbered 10, 16, and 17) were involved in bonds giving anomalous ratios and it was possible to suggest the directions and amounts by which they should be displaced to improve the ratios substantially. These deductions were excellently confirmed by a difference ($F_o - F_c$) synthesis and are now being applied in seeking further refinements.

Acedianthrone

Acedianthrone (IV) has thirty-two π-electrons in a centrosymmetrical molecule; the thirty-second order secular determinant of the molecular-orbital method therefore factorises



(IV*a*) (Numbering used for mathematical calculations.)



(IV*b*) (Ring Index No. 3865.)

at once into two sixteenth-order ones according as $c^i_r = \pm c^i_{33-r}$. The values assumed for the various integrals were the same as for benzanthrone and, by using the methods of expansion and solution given in Part I, the energy levels were obtained which are listed in Table 4 in order of increasing energy, the symbols *S* and *A* indicating respectively the symmetry and antisymmetry of the molecular orbitals and hence the need for the + and − signs relating c^i_r and c^i_{33-r}. Table 5 gives the electron distribution in acedianthrone, while Table 6 gives for the twenty symmetrically independent bonds their mobile orders p_{12}, their lengths L_1 and L_2 derived from these by use of the curves *DGBE* and *DQCE* respectively, and their lengths L_M measured by Friedlander, Goodwin, and Robertson (*loc. cit.*)

TABLE 4. *Molecular-orbital energy levels for acedianthrone.*

i	Symmetry	E_i	i	Symmetry	E_i	i	Symmetry	E_i
1	S	$\alpha + 3{\cdot}0127\beta$	11—14	S, S, A, A	$\alpha + \beta$	24	A	$\alpha - 1{\cdot}307\beta$
2	A	$\alpha + 2{\cdot}9872\beta$	15	S	$\alpha + 0{\cdot}5334\beta$	25	S	$\alpha - 1{\cdot}458\beta$
3	S	$\alpha + 2{\cdot}5613\beta$	16	A	$\alpha + 0{\cdot}5103\beta$	26	A	$\alpha - 1{\cdot}810\beta$
4	A	$\alpha + 2{\cdot}1136\beta$	17	S	α	27	A	$\alpha - 1{\cdot}837\beta$
5	A	$\alpha + 2{\cdot}0422\beta$	18	A	$\alpha - 0{\cdot}598\beta$	28	S	$\alpha - 1{\cdot}923\beta$
6	S	$\alpha + 2{\cdot}0180\beta$	19	S	$\alpha - 0{\cdot}794\beta$	29	S	$\alpha - 2{\cdot}07\beta$
7	S	$\alpha + 1{\cdot}6104\beta$	20	A	$\alpha - 0{\cdot}927\beta$	30	A	$\alpha - 2{\cdot}27\beta$
8	A	$\alpha + 1{\cdot}5337\beta$	21, 22	S, A	$\alpha - \beta$	31	A	$\alpha - 2{\cdot}55\beta$
9	S	$\alpha + 1{\cdot}2216\beta$	23	S	$\alpha - 1{\cdot}089\beta$	32	S	$\alpha - 2{\cdot}66\beta$
10	A	$\alpha + 1{\cdot}1511\beta$						

TABLE 5. *Electron distribution* (q) *in acedianthrone* (*molecular orbital method*)

Atom, numbered according to :			Atom, numbered according to :			Atom, numbered according to :			Atom, numbered according to :		
(IV*a*)	(IV*b*)	q	(IV*a*)	(IV*b*)	q	(IV*a*)	(IV*b*)	q	(IV*a*)	(IV*b*)	q
1	3	0·982	5	5*a*	0·992	9	8*a*	0·996	13	1	0·979
2	4	0·976	6	6	0·987	10	16*c*	1·030	14	2	0·989
3	4*a*	1·016	7	7	0·981	11	16*c*	0·919	15	16*b*	1·093
4	5	0·809	8	8	0·982	12	16*d*	0·996	16 *	O	1·279

* Oxygen.

TABLE 6. *Mobile bond orders* (p) *with calculated and measured bond lengths in acedianthrone* (*molecular-orbital method*).

Bond, numbered according to :						
(IV*a*)	(IV*b*)	p_{12}	L_1	L_2	L_M	ΔL_2
1–2	3–4	0·665	1·390	1·387	1·32	−0·07
1–14	2–3	0·673	1·389	1·384	1·44	0·06
2–3	4–4*a*	0·653	1·393	1·389	1·41	0·02
3–4	4*a*–5	0·301	1·466	1·486	1·40	−0·09
3–12	4*a*–16*d*	0·579	1·409	1·413	1·42	0·01
4–5	5–5*a*	0·307	1·465	1·485	1·49	0
4–16 *	5–O	*0·862*	*1·195*	*1·195*	*1·20*	*0*
5–6	5*a*–6	0·634	1·397	1·395	1·41	0·01
5–10	5*a*–16*e*	0·580	1·409	1·413	1·37	−0·04
6–7	6–7	0·654	1·393	1·389	1·35	−0·04
7–8	7–8	0·654	1·393	1·389	1·38	−0·01
8–9	8–8*a*	0·621	1·400	1·399	1·42	0·02
9–10	8*a*–16*e*	0·542	1·418	1·427	1·39	−0·04
9–18	8*a*–8*b*	0·396	1·450	1·476	1·48	0
10–11	16*c*–16*e*	0·427	1·443	1·471	1·49	0·02
11–12	16*c*–16*d*	0·442	1·440	1·467	1·49	0·02
11–15	16*b*–16*c*	0·622	1·400	1·399	1·41	0·01
12–13	1–16*d*	0·608	1·403	1·403	1·41	0·01
13–14	1–2	0·686	1·386	1·381	1·30	−0·08
15–18	8*b*–16*b*	0·507	1·426	1·440	1·59	0·15

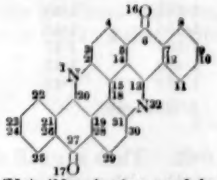
* Oxygen.

who consider them to be subject to an error of $\pm 0{\cdot}06$, owing to the overlap of the molecules in the *b*-axis projection and to the non-resolution of certain atoms in other projections; $\Delta L_2 = L_M - L_2$ is also included. Neither the figures L_1 nor the values of ΔL are quite the same as those recorded in the above paper in which the calculated lengths were derived from a curve not quite identical with *DGBE* but ΔL of that paper is nearly $L_M - L_1$ of this. As these authors hope to re-examine this compound by *X*-rays to resolve the rather large discrepancies between a few of the observed and the calculated bond lengths, detailed comment is unnecessary at present. Again the bond lengths ought to be accurate to $\pm 0{\cdot}03$ Å except for C–C bonds adjacent to the carbonyl groups. Of the twenty symmetrically independent interatomic distances it is very satisfactory to note that twelve have $|\Delta L|$ not greater than 0·03 Å and that only five have $|\Delta L|$ equal to or greater than the indicated experimental uncertainty of 0·06 Å. Three of these are the bonds 2–1, 1–14, 14–13, and it is not unreasonable to attribute part of their discrepancies to the failure to resolve atoms 1 and 14,

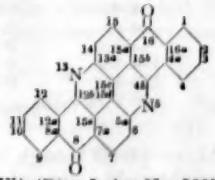
especially as ΔL is negative for bonds 1–2 and 13–14 but positive for 1–14. Indeed bonds 1–2 and 13–14 are quoted as shorter than pure double bonds so that re-examination of their lengths is certainly called for. A similar remark applies to bond 3–4, which is recorded as being of about average aromatic length as compared with 1·49 Å required by the present calculations and 1·50 Å if regarded as a single bond in accordance with the simplest valence-bond approximation. As for bond 15–18, there is no doubt that a little of the discrepancy noted must be due to failure to allow for either a difference in hybridisation or a reduction of overlap in the five-membered rings where not all the angles can have the value of 120° required if maximum overlap of sp^2 orbitals is to occur. Change of hybridisation cannot be great since the molecule is planar. In chemical language we may say that this portion of the molecule must show strain tending to lengthen the central bond and in so far as the present calculations make no allowance for this they are inadequate. The simple molecular orbital theory used implies that all bonds in which the π-electrons can participate must be shorter than pure single bonds, so that it is difficult to believe that an allowance for strain (change of hybridisation or reduction of overlap) can increase the calculated interatomic distance from 1·44 to 1·53 Å, the minimum allowed by the *X*-ray measurements. Again further discussion must await refinement of the *X*-ray results and perhaps also of these calculations.

Flavanthrone

Flavanthrone (V) has thirty-two π-electrons in its centrosymmetrical molecule and again the secular determinant factories into two sixteenth-order ones. The values of the various integrals in the secular equations were supposed to be the same as in benzanthrone with the addition of a Coulomb integral for nitrogen of $\alpha + \frac{1}{2}\beta$, the exchange integral between adjacent carbon and nitrogen being set equal to β as between neighbouring carbon atoms.



(V*a*) (Numbering used for mathematical calculations.)



(V*b*) (Ring Index No 3887)

On expansion and solution by the methods of Part I, the secular determinant gave first the values recorded in Table 7 for the sixteen lowest energy levels in increasing order of energy then the electron distribution (Table 8) and (Table 9) the bond orders and interatomic distances L_1 and L_2. Also in Table 9 are the interatomic distances L_M measured by Stadler (*loc. cit.*) along with $\Delta L_2 = L_M - L_2$.

If only the calculated interatomic distances are considered the same general comments could be made as for benzanthrone (subject to modifications caused by the nitrogen) but it is more useful to compare observed and calculated bond lengths, noting that as before the calculations should not be in error by more than *ca.* 0·03 Å, except perhaps for bonds attached to the keto-groups and for C–N bonds. It is then very satisfactory to find that for fifteen of the twenty symmetrically independent bonds $|\Delta L_2| < 0{\cdot}03$ Å. The calculated standard deviation of the observed co-ordinates is 0·032 Å, that of the bond lengths is thus 0·05 Å; seventeen of the bonds have $|\Delta L| < 0{\cdot}05$ Å. Of the others, bond 1–20 (equivalent to 13–32) involves the nitrogen (1 or 32) but even so is remarkably short; however, bond

Table 7. *Lowest energy levels in flavanthrone (molecular-orbital method).*

i	Symmetry	E_i	*i*	Symmetry	E_i	*i*	Symmetry	E_i
1	*S*	$\alpha + 3{\cdot}01149\beta$	6	*A*	$\alpha + 1{\cdot}9726\beta$	11	*A*	$\alpha + 1{\cdot}1120\beta$
2	*A*	$\alpha + 2{\cdot}9849\beta$	7	*A*	$\alpha + 1{\cdot}8341\beta$	12, 13	*S*, *A*	$\alpha + \beta$
3	*S*	$\alpha + 2{\cdot}5532\beta$	8	*S*	$\alpha + 1{\cdot}4578\beta$	14	*A*	$\alpha + 0{\cdot}8552\beta$
4	*A*	$\alpha + 2{\cdot}22451\beta$	9	*S*	$\alpha + 1{\cdot}3170\beta$	15	*S*	$\alpha + 0{\cdot}7984\beta$
5	*S*	$\alpha + 2{\cdot}0507\beta$	10	*S*	$\alpha + 1{\cdot}2729\beta$	16	*A*	$\alpha + 0{\cdot}52748\beta$

TABLE 8. *Electron distribution* (q) *in flavanthrone.*

Atom, numbered according to: (Va)	(Vb)	q	Atom, numbered according to: (Va)	(Vb)	q	Atom, numbered according to: (Va)	(Vb)	q	Atom, numbered according to: (Va)	(Vb)	q
1†	13†	1·209	5	15*a*	1·004	9	2	0·984	13	4*b*	0·892
2	13*a*	0·951	6	16	0·813	10	3	0·984	14	15*b*	0·993
3	14	0·987	7	16*a*	1·003	11	4	0·977	15	15*c*	0·980
4	15	0·964	8	1	0·874	12	4*a*	0·992	16*	O	1·290

* Oxygen. † Nitrogen.

TABLE 9. *Mobile bond orders* (p) *with calculated and measured bond lengths in flavanthrone (molecular-orbital method).*

Bond, numbered as: (Va)	(Vb)	p_{12}	L_1	L_2	L_M	ΔL_2
† 1–2	13–13*a*	*0·515*	*1·374*	*1·374*	*1·37*	*0*
† 1–20	12*b*–13	*0·489*	*1·379*	*1·379*	*1·30*	*−0·08*
2–3	13*a*–14	0·583	1·408	1·412	1·44	0·03
2–15	13*a*–15*c*	0·515	1·424	1·438	1·43	−0·01
3–4	14–15	0·682	1·387	1·382	1·37	−0·01
4–5	15–15*a*	0·628	1·399	1·397	1·42	0·02
5–6	15*a*–16	0·307	1·465	1·485	1·50	0·01
5–14	15*a*–15*b*	0·593	1·406	1·409	1·33	−0·08
6–7	16–16*a*	0·303	1·465	1·486	1·54	0·05
6–16*	16–O	*0·866*	*1·194*	*1·194*	*1·21*	*0·02*
7–8	1–16*a*	0·645	1·395	1·392	1·40	0·01
7–12	4*a*–16*a*	0·585	1·408	1·411	1·40	−0·01
8–9	1–2	0·665	1·390	1·387	1·36	−0·03
9–10	2–3	0·655	1·392	1·389	1·46	0·07
10–11	3–4	0·675	1·389	1·384	1·41	0·03
11–12	4–4*a*	0·614	1·401	1·401	1·40	0
12–13	4*a*–4*b*	0·476	1·433	1·455	1·48	0·02
13–14	4*b*–15*b*	0·278	1·470	1·487	1·47	−0·02
14–15	15*b*–15*c*	0·536	1·419	1·430	1·43	0
15–18	15*c*–15*d*	0·511	1·421	1·433	1·48	0·05

* Oxygen. † Nitrogen.

12–13 has $\Delta L = +0{\cdot}02$ though bond 13–14 has $\Delta L = 0{\cdot}02$. Thus a small displacement of atom 13 might yield a general improvement in these lengths although the centre marked for this atom seems to be that indicated by the contours of the published Fourier projection. Bonds 9–10 and 15–18 are much too long, although since the latter contains the centre of symmetry only half its length can be measured: it is therefore less reliable. However, too great significance should not be attached to the few large discrepancies, since the *X*-ray examination was not effected primarily to measure the interatomic distances with very great accuracy.

Conclusion.—Although there is some uncertainty as to the magnitude of the Coulomb and exchange parameters in hetero-compounds, and although all wave-mechanical derivations of bond lengths in molecules as large as those discussed here are approximations, it is reasonable to conclude that, provided there are not more than about two hetero-atoms to fourteen carbon atoms, bond lengths can be predicted to about $\pm 0{\cdot}03$ Å in these large polynuclear compounds. It should therefore be possible to correlate calculated and observed bond lengths while *X*-ray work is in progress and so help in determining how to adjust molecular models in refining atomic co-ordinates (as with benzanthrone).

The interest of Professor J. M. Robertson, F.R.S., in this work is gratefully acknowledged, while special thanks are offered to Professor C. A. Coulson, F.R.S., and Professor V. Vand for much helpful discussion and advice.

CHEMISTRY DEPARTMENT, UNIVERSITY OF GLASGOW. [*Received, November 22nd*, 1954.]

2-*Mercaptoglyoxalines. Part IX.* The Preparation of* 1 : 5-*Disubstituted* 2-*Mercaptoglyoxalines from* α-*Amino-acids.*

By ALEXANDER LAWSON and H. V. MORLEY.

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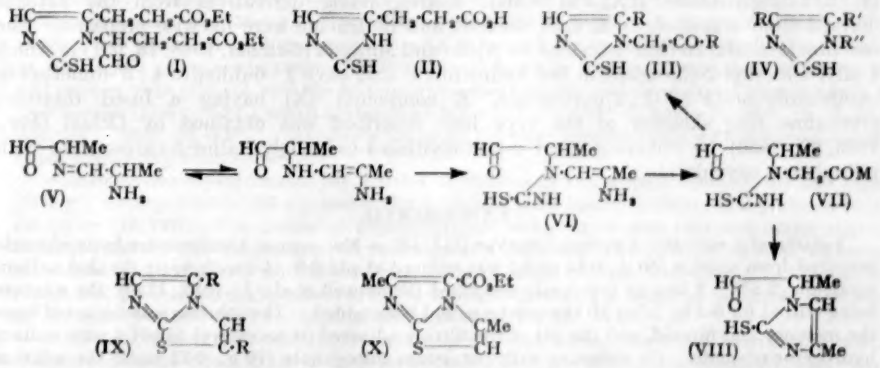
The reduction of α-amino-acid esters by the Akabori procedure and condensation of the resulting carbonyl compounds with thiocyanate at pH 4 gives 1 : 5-disubstituted 2-mercaptoglyoxalines (III). The constitution of these compounds is proved by synthesis of the derivative (IV; R = H, R′ = Me, R″ = Pr^n) obtained by Wolff–Kishner reduction of (III; R = Me). These ketones (III) have been converted into thiazolo(3′ : 2′-1 : 2)glyoxalines (IX) by ring closure.

IN Part VIII * it was reported that reduction of ethyl glutamate by sodium amalgam under less acid conditions than were used in the Akabori procedure (*Ber.*, 1933, **67**, 151), followed by ring closure with thiocyanate, gave a substance believed to be the glyoxaline (I), or the 1 : 4-disubstituted isomer, in addition to the expected mercaptoglyoxalinylpropionic acid (II). The essential condition for the formation of these disubstituted mercaptoglyoxalines is that the condensation with thiocyanate should be carried out at pH 4 and they are then formed almost exclusively. At higher pH values, excessive decomposition with blackening takes place, and under more acid conditions (pH 2) only the mercaptoglyoxaline having no *N*-substituent is isolated.

To determine the structure of these disubstituted mercaptoglyoxalines the product obtained from alanine was more closely studied, as being the most readily accessible. This product gave the iodoform reaction, showing it to be, not the aldehyde, but the ketone (III; R = Me) or the 1 : 4-disubstituted isomer. It could not, however, be converted into



the sulphur-free glyoxaline by treatment with Raney nickel in boiling ethanol (Cook, Downer, and Heilbron, *J.*, 1948, 1262), and attempts at reductive fission of the *N*-acetonyl group by sodium in liquid ammonia (Heath, Lawson, and Rimington, *J.*, 1951, 2218) gave only unchanged starting material. The reduction failed also with 2-mercapto-1-methylglyoxaline. The product from alanine was, however, reduced by the Wolff–Kishner procedure used by Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to a product identical with 2-mercapto-5-methyl-1-*n*-propylglyoxaline (IV; R = H, R′ = Me, R″ = Pr^n) synthesised from α-*n*-propylaminopropionaldehyde diethyl acetal and ammonium thiocyanate.

2-Mercapto-4-methyl-1-*iso*propylglyoxaline (IV; R = Me, R′ = H, R″ = Pr^i) has been synthesised from α-*iso*thiocyanatopropionaldehyde diethyl acetal and *iso*propylamine,

* Part VIII, *J.*, 1954, 3283.

and also the corresponding 1 : 5-disubstituted glyoxaline (IV; R = H, R′ = Me, R″ = Pr^i) from α-*iso*propylaminopropionaldehyde diethyl acetal.

In view of the above identification it appears that the product obtained from alanine ethyl ester is 1-acetonyl-2-mercapto-5-methylglyoxaline (III; R = Me). This substance probably arises as a result of the intermediate formation from two molecules of the amino-aldehyde of the Schiff's base (V) which would isomerise, not as suggested in Part VIII (*loc. cit.*), but by an imino-enamine rearrangement which would be made irreversible by the reaction with the thiocyanate. The 1 : 2-unsaturated amine (VI) so formed would then be spontaneously deaminated, in accordance with the known instability of such compounds, to give the ketone (VII). Deamination of aminoacetaldehyde in warm slightly acid solution was observed by Fischer (*Ber.*, 1893, **26**, 194). The keto-aldehyde (VII) could cyclise to give either the 1-1′-formylethylglyoxaline (VIII) or the acetonyl derivative (III; R = Me). No aldehyde was isolated from the reaction and indeed it might be expected that the intermediate thiourea would cyclise more readily by reaction with the aldehyde than with the ketone group. The considerable darkening of the reaction mixture and the tar formation may indicate that an alternative ring closure also takes place to some extent.

Disubstituted mercaptoglyoxalines analogous to that prepared from alanine were obtained from α-aminobutyric acid (III; R = Et), leucine (III; R = Bu^i), norleucine (III; R = Bu^n), phenylalanine (III; R = CH_2Ph), and glutamic acid (III; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) (cf. Part VIII, *loc. cit.*). It has not been possible to isolate the corresponding derivative from glycine.

When 1-acetonyl-2-mercapto-5-methylglyoxaline (III; R = Me) was refluxed with concentrated hydrochloric acid, there was formed by loss of water a low-melting, water-insoluble, base, having no free thiol group. The formation of this substance is best accounted for on the basis of loss of water of the enol form of the ketone with the mercapto-hydrogen atom to give the diheterocyclic derivative 5 : 5′-dimethylthiazolo-(3′ : 2′-1 : 2)glyoxaline (IX; R = Me). Corresponding derivatives from the ketones derived from α-aminobutyric acid, leucine, and norleucine were likewise prepared. The reaction is similar to that described by Ajello and Miraglia (*Gazzetta*, 1948, **78**, 921) in which 1-allyl-4-methyl-2-thiouracil in hot hydrochloric acid gave 1 : 6-dihydro-4 : 5′-dimethyl-6-oxothiazolidino-(3′ : 2′-1 : 2)pyrimidine. A compound (X) having a fused thiazole–glyoxaline ring skeleton of the type here described was obtained by Ochiai (*Ber.*, 1936, **69**, 1650) by refluxing ethyl 2-acetonylthio-4-methylglyoxaline-5-carboxylate with phosphorus oxychloride.

Experimental

1-*Acetonyl-2-mercapto-5-methylglyoxaline* (III; R = Me).—DL-α-Alanine ester hydrochloride prepared from alanine (50 g., 0·56 mole) was reduced at pH 2·0—4·5 with finely divided sodium amalgam (2·5%; 2 kg.) as previously described (Bullerwell *et al.*, *J.*, 1952, 1350), the mixture being stirred for 0·5 hr. after all the amalgam had been added. The solution was decanted from the mercury and filtered, and the pH of the filtrate adjusted (if necessary) to pH 4 with sodium hydrogen carbonate. On refluxing with potassium thiocyanate (70 g., 0·72 mole) the solution became dark brown, and after 0·75 hr. it was concentrated, at atmospheric pressure, until crystals began to appear. The dark brown product was filtered off and crystallised from water (charcoal), to give 1-*acetonyl-2-mercapto-5-methylglyoxaline*, white blades, m. p. 182—183° (16·5 g., 35%) (Found : C, 49·4; H, 6·0; N, 16·6; S, 18·6. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9; N, 16·5; S, 18·7%). The absorption maximum was at 2580 Å (ε = 16,600) in H_2O and at 2740 Å (ε 15,900) in $CHCl_3$. The compound was soluble in chloroform or ethyl acetate, sparingly so in water or ethanol, and insoluble in ether. It gave the iodoform reaction. The *semicarbazone* had m. p. 250—251° (decomp.) (Found : C, 42·5; H, 5·9. $C_8H_{13}ON_5S$ requires C, 42·3; H, 5·7%). The *oxime* had m. p. 210—211° (decomp.) (Found : C, 45·5; H, 6·1; N, 22·9. $C_7H_{11}ON_3S$ requires C, 45·4; H, 6·0; N, 22·7%). $\lambda_{max.}$ = 2660 Å (ε = 15,500) in EtOH.

Adding the thiocyanate to the amino-aldehyde solution at pH *ca.* 3·0 gave a mixture of 2-mercapto-4(5)-methylglyoxaline (28·4 g., 44·5%), m. p. 246° (decomp.), and 1-acetonyl-2-mercapto-5-methylglyoxaline (7·2 g., 15%), from which the ketone was extracted with chloroform.

5-Ethyl-2-mercapto-1-2′-oxobutylglyoxaline (III; R = Et).—DL-α-Aminobutyric acid (10 g.) was esterified and the ester hydrochloride reduced as above with sodium amalgam (2·5%; 400 g.). The resulting solution was condensed at pH 3·8 with ammonium thiocyanate (12 g.). Refluxing for 0·75 hr. and evaporation of the solution to a small volume gave *5-ethyl-2-mercapto-1-2′-oxobutylglyoxaline* (colourless needles) mixed with tar. After repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) the substance had m. p. 118—120° (1·4 g., 14·6%) (Found: C, 55·0; H, 6·9. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1%).

5-n-Butyl-2-mercapto-1-2′-oxohexylglyoxaline (III; R = Bu^n).—DL-α-Norleucine (10 g.) was esterified and reduced as for alanine, the ammonium thiocyanate (9·0) being added at pH 3·5. The solution on refluxing for 0·5 hr. deposited a red oil which solidified on cooling and was filtered off (5·7 g.). It was possible to separate the mixture by fractional crystallisation from ether or, better, by extraction with hot light petroleum (b. p. 60—80°). The petroleum deposited *5-n-butyl-2-mercapto-1-2′-oxohexylglyoxaline*, needles (1·8 g., 18·6%), m. p. 98—100° (Found: C, 61·0; H, 8·5; N, 11·0; S, 12·4. $C_{12}H_{22}ON_2S$ requires C, 61·4; H, 8·65; N, 11·0; S, 12·6%). The insoluble residue, crystallised from water, gave 4(5)-butyl-2-mercaptoglyoxaline (4·2 g., 35%), m. p. 125—127°.

5-isoButyl-2-mercapto-1-(4-methyl-2-oxopentyl)glyoxaline (III; R = Bu^i).—L-Leucine (10 g.) was treated as above, the ammonium thiocyanate (9·0 g.) being added at pH 4. The solution, which darkened when heated, deposited on cooling *5-isobutyl-2-mercapto-1-(4-methyl-2-oxopentyl)glyoxaline* (3·5 g.). Crystallisation from aqueous ethanol and then from ethanol gave colourless needles, m. p. 153—154° (1·1 g., 11·3%) (Found: C, 60·4; H, 8·6; N, 11·1. $C_{12}H_{22}ON_2S$ requires C, 61·4; H, 8·65; N, 11·0%).

5-Benzyl-2-mercapto-1-(2-oxo-3-phenylpropyl)glyoxaline (III; R = CH_2Ph).—DL-β-Phenylalanine (10 g.) was esterified and reduced as above. Precipitation commenced as soon as the ammonium thiocyanate (9·0 g.) was added, but heating was continued for 0·5 hr. The product partially dissolved in boiling water from which 4(5)-benzyl-2-mercaptoglyoxaline (3·6 g., 31%), m. p. 220—223° (decomp.), crystallised. The insoluble residue crystallised from ethyl acetate to give the *ketone*, felted needles (0·8 g., 7·7%), m. p. 162—163° (Found: C, 70·7; H, 5·6; N, 8·4; S, 9·8. $C_{19}H_{18}ON_2S$ requires C, 70·8; H, 5·6; N, 8·7; S, 9·9%).

α-iso*Propylaminopropionic Acid*.—To *iso*propylamine (35·4 g., 0·6 mole) in water (20 ml.), α-bromopropionic acid (30·6 g., 0·2 mole) was added slowly, with ice-cooling and stirring. The mixture was then kept at room temperature for 68 hr. and the excess of *iso*propylamine removed by distillation at reduced pressure. After several hours at 0°, the precipitate was filtered off and washed with ethanol, and the α-iso*propylaminopropionic* acid crystallised from ethanol, to give needles (13·6 g., 52%) which sublimed at 295—300° (Found: C, 55·0; H, 10·0. $C_6H_{13}O_2N$ requires C, 55·0; H, 9·9%). Attempts to reduce the ester hydrochloride with sodium amalgam failed to give any amino-aldehyde.

α-iso*Propylaminopropionaldehyde Diethyl Acetal*.—α-Bromopropionaldehyde diethyl acetal (31·8 g.), *iso*propylamine (63 g.), and ethanol (20 ml.) were heated together in a pressure-bottle for 10 hr. at 100°. The excess of *iso*propylamine and ethanol was removed under slightly reduced pressure and the residue was taken up in a little water, saturated with solid potassium carbonate, and extracted with chloroform. The chloroform layer was dried (K_2CO_3) and on removal of the solvent the residue was fractionated, to give 14·2 g. (50%) of the *acetal*, b. p. 86—88°/26 mm. (Found: N, 7·2. $C_{10}H_{23}O_2N$ requires N, 7·4%).

2-Mercapto-5-methyl-1-isopropylglyoxaline.—α-*iso*Propylaminopropionaldehyde diethyl acetal (2·4 g.), potassium thiocyanate (2·4 g.), 2N-hydrochloric acid (10 ml.), and ethanol (10 ml.) were heated under reflux for 10 hr. The solution was evaporated to dryness under reduced pressure, and extracted with acetone. Evaporation of the acetone left a dark-brown oil which was taken up in 3N-sodium hydroxide and decolorised with charcoal. Acidification, extraction with chloroform, and removal of the solvent gave a light yellow solid *glyoxaline* which, crystallised from ether or light petroleum (b. p. 60—80°), had m. p. 198—199° (0·25 g., 8%) (Found: C, 54·2; H, 7·7; N, 17·7. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0%).

α-iso*Thiocyanatopropionaldehyde Diethyl Acetal*.—A mixture of the α-amino-acetal (10 g.), carbon disulphide (6·7 g.), 5N-sodium hydroxide (15 ml.), and water (34 ml.) was warmed gently and shaken until dissolution was effected. The solution was cooled to 0° and treated with an ice-cold solution of basic lead acetate (40 ml.; 25% w/v) with stirring and then an ice-cold solution of normal lead acetate (20 g.) in water (50 ml.) was gradually added. The mixture was kept cold for 0·5 hr., then gradually warmed on the steam-bath with stirring. The coloured precipitate gradually blackened, and the product was isolated by steam-distillation and extraction of the distillate with ether. The ethereal layer was dried (K_2CO_3), the solvent

removed, and the light yellow pungent oil fractionated, to give 9·4 g. (73·5%) of the colourless *isothiocyanato-acetal*, b. p. 125°/27 mm. (Found: C, 49·3; H, 7·9; N, 7·3. $C_5H_{15}O_2NS$ requires C, 50·8; H, 7·9; N, 7·4%).

2-Mercapto-4-methyl-1-isopropylglyoxaline.—The foregoing product (3·8 g.), *iso*propylamine (2 g.), and ethanol (5 ml.) were heated on the water-bath for 30 min. (heat was evolved on initial mixing). The solvent was removed and the remaining oil refluxed with 30% sulphuric acid (10 c.c.) for 10 hr. The cooled solution was extracted with chloroform, and the dried chloroform layer was evaporated to give a brown oil, which was extracted with ether. Removal of the solvent and crystallisation from light petroleum (b. p. 60—80°) gave *2-mercapto-4-methyl-1-isopropylglyoxaline* (white needles; 0·3 g., 9·5%), m. p. 156—158° (Found: C, 54·3; H, 7·7; N, 17·7. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0%).

α-n-Propylaminopropionaldehyde Diethyl Acetal.—The α-bromo-acetal (31·8 g.), *n*-propylamine (63 g.), and ethanol (20 ml.) were heated together in a pressure-bottle for 12 hr. at 100°. The mixture was worked up as for the *iso*propyl derivative. The *product* was a colourless oil (12·9 g., 45%), b. p. 98°/30 mm. (Found: C, 63·4; H, 12·0; N, 7·4. $C_{10}H_{23}O_2N$ requires C, 63·5; H, 12·1; N, 7·4%).

2-Mercapto-5-methyl-1-n-propylglyoxaline.—*Method* I. *α-n*-Propylaminopropionaldehyde diethyl acetal (3·8 g.), ammonium thiocyanate (2·4 g.), 2N-hydrochloric acid (20 ml.), and ethanol (5 ml.) were refluxed for 3 hr. Next morning the crystals which had separated were collected and washed with water. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave *2-mercapto-5-methyl-1-n-propylglyoxaline*, broad needles (2·6 g., 84%), m. p. 166—167° (Found: C, 54·5; H, 7·6. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7%). This was identical (mixed m. p.) with the product obtained from 1-acetonyl-2-mercapto-5-methylglyoxaline by Wolff–Kishner reduction.

Method II. 1-Acetonyl-2-mercapto-5-methylglyoxaline (0·75 g.), hydrazine hydrate (1 ml., 90% w/w), potassium hydroxide (1·4 g.), and ethylene glycol (50 ml.) were refluxed for 1·5 hr. The water was then distilled off until the temperature reached 190° and the solution was refluxed for a further 5 hr. The cooled solution was acidified (some hydrogen sulphide was given off) and extracted with chloroform (2 × 50 ml.). On removal of the chloroform, the gummy residue was crystallised first from ether and then from benzene–light petroleum (b. p. 60—80°), to give the *glyoxaline* (0·23 g., 30%), m. p. 165—167° (Found: C, 53·7; H, 7·8; N, 18·1; S, 20·4. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0; S, 20·5%).

5 : 5′-Dimethylthiazolo(3′ : 2′-1 : 2)glyoxaline (IX; R = Me).—1-Acetonyl-2-mercapto-5-methylglyoxaline (0·5 g., 0·003 mole) was refluxed with concentrated hydrochloric acid (5 ml.) for 0·5 hr., cooled, and made alkaline (pH 10). The oily product solidified at 0° and crystallised from light petroleum (b. p. 60—80°) to give the *thiazologlyoxaline* as white diamond-shaped plates, m. p. 88—89° (yield quantitative) (Found: C, 55·3; H, 5·5; N, 17·9; S, 20·4. $C_7H_8N_2S$ requires C, 55·3; H, 5·3; N, 18·4; S, 21·0%), which was very soluble in organic solvents, but insoluble in water. Light absorption: max. at 2480 Å (ε 5400) in EtOH.

5 : 5′-Diisobutylthiazolo(3′ : 2′-1 : 2)glyoxaline (IX; R = Bu^i).—*5-iso*Butyl-2-mercapto-1-(4-methyl-2-oxopentyl)glyoxaline (0·35 g., 0·0014 mole) on similar treatment gave a white solid which crystallised from light petroleum (b. p. 60—80°) to give the *5 : 5′-diisobutyl* compound, m. p. 96—98°, in quantitative yield (Found: C, 65·7; H, 8·4; N, 11·8. $C_{13}H_{20}N_2S$ requires C, 66·1; H, 8·5; N, 11·9%).

5 : 5′-Di-n-butylthiazolo(3′ : 2′-1 : 2)glyoxaline (IX; R = Bu^n).—*5-n*-Butyl-2-mercapto-1-2′-oxohexylglyoxaline (0·15 g., 0·0006 mole) on similar treatment gave an oil which did not solidify at 0° and from which *5 : 5′-di-n-butylthiazolo(3′ : 2′-1 : 2)glyoxaline picrate* was obtained as yellow needles (0·23 g., 84%), m. p. 185—186° (from ethanol) (Found: C, 48·7; H, 5·0; N, 15·3. $C_{19}H_{23}O_7N_5S$ requires C, 49·0; H, 5·0; N, 15·1%).

5 : 5′-Diethylthiazolo(3′ : 2′-1 : 2)glyoxaline (IX; R = Et).—5-Ethyl-2-mercapto-1-2′-oxobutylglyoxaline (0·6 g., 0·003 mole) on similar treatment gave an oil (quantitative yield) which did not crystallise. It readily afforded *5 : 5′-diethylthiazolo(3′ : 2′-1 : 2)glyoxaline picrate*, yellow needles (from ethanol), m. p. 238—240° (decomp.) (Found: C, 44·0; H, 3·8. $C_{15}H_{15}O_7N_5S$ requires C, 44·0; H, 3·7%).

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ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
8 HUNTER STREET, LONDON, W.C.1.

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Raman Effect and Solvent Extraction. Spectrum of the $InBr_4^-$ *Ion.*

By L. A. Woodward and P. T. Bill.

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Molar aqueous solutions of indium bromide containing hydrobromic acid at concentrations up to 6N are extracted with ether or *iso*butyl methyl ketone. The extracts all show the following Raman frequencies (cm.$^{-1}$) due to solute: 55, strong, sharp, depolarised; 79, strong, sharp, depolarised; 197, very strong, sharp, polarized; and 239, medium, slightly diffuse, depolarized. Reasons are given for ascribing this spectrum to the regular tetrahedral $InBr_4^-$ ion. The Raman spectra of the aqueous solutions before extraction show a band whose position varies with hydrobromic acid concentration, but no lines characteristic of $InBr_4^-$.

The extraction of indium by organic solvents from aqueous solutions of indium bromide containing hydrobromic acid has been studied recently by Irving and Rossotti (*J.*, in the press), with initial indium concentrations from tracer values up to nearly 0·1M. Their results provide evidence that the acido-complex $HInBr_4$ predominates in the organic phase, and they suggest that this complex may be present as a solvated ion pair $(H^+)(InBr_4^-)$.

The Raman effect provides a very direct method for the detection of covalently linked species and, in favourable cases, for the determination of their structure. The present paper gives an account of the application of this method to systems of the kind referred to above.

Raman Spectra of Organic Extracts.—Owing to the small intensity of Raman scattering, the concentration of indium in the aqueous phase before extraction was made molar in all the experiments. This is higher than was investigated by Irving and Rossotti (*loc. cit.*). The principal solvent used for extraction was ethyl ether, but some experiments were also made with *iso*butyl methyl ketone. All extractions were carried out at room temperature. It was found that the amount of extraction of indium by ether from M-aqueous indium bromide solution containing no added hydrobromic acid was negligible. Table 1 shows the Raman frequencies ($\Delta\nu$) observed for the solute in organic extracts from aqueous solutions containing different concentrations of hydrobromic acid. The Raman lines due to the solute were easily distinguishable from the solvent lines, all of which have

Table 1. *Raman spectra of solute in organic extracts.*

Normality of HBr before extraction	2	4	4	6
Solvent	ether	ether	ketone	ether
Observed Raman frequencies (cm.$^{-1}$)	56	54	55	56
	79	77	79	80
	197	196	197	198
	238	239	240	239

considerably higher frequencies. The spectra of the pure solvents were photographed for comparison.

Within the accuracy of the measurements the spectra of all the extracts are identical. The two lines of lowest frequency lie close to the exciting line, but with suitably chosen exposure times they could be clearly discerned and accurately measured. They were observable not only as Stokes lines excited by Hg 4358 Å, but also as both Stokes and anti-Stokes lines excited by Hg 4046 Å.

The states of polarization of the lines were investigated by the method of polarized incident light (Rank and Kagarise, *J. Opt. Soc. Amer.*, 1950, **40**, 89), a photoelectric recording instrument being used and with cylinders of Polaroid surrounding the Raman tube. It was found that the line with $\Delta\nu = 197$ cm.$^{-1}$ is very strongly polarized, whereas the other three are all strongly depolarized. The mean frequencies, estimated relative intensities, appearances of lines, and states of polarization are shown in Table 2. The number of observed lines and their states of polarization provide strong evidence that the spectrum is

to be ascribed to a regular tetrahedral species of type XY_4. There can be little doubt that the species in question is the $InBr_4^-$ ion. This view is in agreement with Irving and Rossotti's conclusion (*loc. cit.*) that the predominant species in the organic phase is the acido-complex $HInBr_4$, and our observations show that this complex must be regarded as an ion-pair of the type $(H^+)(InBr_4^-)$. The purely electrostatic binding between the

TABLE 2. *Raman spectrum of* $InBr_4^-$.

cm.$^{-1}$	Intensity	Appearance	Polarization	cm.$^{-1}$	Intensity	Appearance	Polarization
55	strong	sharp	depolarized	197	very strong	sharp	polarized
79	strong	sharp	depolarized	239	medium	slightly diffuse	depolarized

two ions will not be expected to show a Raman effect (George, Rolfe, and Woodward, *Trans. Faraday Soc.*, 1953, **49**, 375). Further support was obtained by chemical analysis of the organic extracts. In all cases it was found that $[Br]/[In] = 4{\cdot}0 \pm 0{\cdot}1$.

It is noteworthy that the singly charged $InBr_4^-$ ion is isoelectronic with the uncharged molecule $SnBr_4$ and the doubly charged ion $CdBr_4^{=}$, and it is of interest to compare the fundamental vibrational frequencies of these three species (see Table 3). The values for

TABLE 3. *Fundamental vibrational frequencies (cm.*$^{-1}$*) of isoelectronic species* XBr_4.

	ν_3 (F_2)	ν_4 (F_2)	ν_1 (A_1)	ν_2 (E)
$SnBr_4$	64	88	220	279
$InBr_4^-$	55	79	197	239
$CdBr_4^{=}$	53	62	166	183

$SnBr_4$ are those quoted by Herzberg ("Molecular Spectra and Molecular Structure," van Nostrand Co., New York, 1945, Vol. II, p. 167); those for $CdBr_4^{=}$ are from the observations of Delwaulle, François, and Wiemann (*Compt. rend.*, 1939, **208**, 1818) and Rolfe, Sheppard, and Woodward (*Trans. Faraday Soc.*, 1954, **50**, 1275). It is seen that the frequencies observed in the present work all lie between the corresponding ones for $SnBr_4$ and $CdBr_4^{=}$, and this may be taken as further support for the view that the species with which we are concerned is $InBr_4^-$. The assignment of the observed frequencies to the vibrational modes follows the assignment for $SnBr_4$ (Herzberg, *op. cit.*) and is included in Table 3. In particular we may remark that the assignment of 197 cm.$^{-1}$ to the totally symmetrical (A_1) "breathing" mode (frequency ν_1) is in harmony with the observation that the corresponding Raman line is polarized.

From Table 3 it is seen that all the fundamental frequencies become progressively smaller as we pass from $SnBr_4$ to $InBr_4^-$ and then to $CdBr_4^{=}$. As far as the "breathing" frequencies ν_1 are concerned this indicates that the stretching force constant k of the metal–bromine bond decreases in the same order. The values of $10^{-5}k$ calculated on the basis of a simple valency force field are: $SnBr_4$, 2·28; $InBr_4^-$, 2·16; and $CdBr_4^{=}$, 1·98 dynes per cm. Force constants of these isoelectronic species derived from more general force fields will be discussed in a later publication.

Raman Spectra of Aqueous Solutions before Extraction.—The Raman spectrum of molar aqueous indium bromide solution without added hydrobromic acid was found to consist of a single band of medium intensity. Its width is approximately 30 cm.$^{-1}$ and its centre is at about $\Delta\nu = 205$ cm.$^{-1}$. With increasing concentration of added acid the position of the band centre moves progressively to lower $\Delta\nu$ values until in the strongest acid used (6N) it is at approximately 185 cm.$^{-1}$. The exact position of the centre of the band is difficult to judge precisely, but the gradual displacement with increasing acid concentration is quite certain. The band width and intensity remain approximately constant over the range of acid concentrations investigated. In some of the spectrograms there was an indication of a very feeble line at about $\Delta\nu$ 140 cm.$^{-1}$ excited by Hg 4358 Å; but its existence must be regarded as doubtful.

The broadness of the band may well be due to the simultaneous presence of several different species (such as $InBr^{++}$, $InBr_2^+$, $InBr_3$) in equilibrium. The stretching-mode frequencies of all such species will be expected to lie in the same region as ν_1 of $InBr_4^-$

and, since Raman lines in aqueous solutions are often somewhat diffuse, the observed band may be due to unresolved overlapping. Its apparent gradual displacement with increasing addition of hydrobromic acid would then be explicable as due to a progressive displacement of the equilibria between the various species involved, with corresponding alteration of the intensities of their contributions to the band. From the evidence of the Raman spectra it is not possible to say what species are present in the aqueous solutions. Comparison with the intense " regular tetrahedral XY_4 " pattern of the spectra of the organic extracts shows, however, that the species ($InBr_4^-$) which predominates in the organic layer after extraction cannot have been present in appreciable concentration in the aqueous solution before extraction.

Experimental

Preparation of Aqueous Solutions.—Weighed quantities of finely sliced indium (99·7% pure, supplied by Messrs. Johnson Matthey and Co.) were dissolved in the appropriate calculated quantities of hydrobromic acid, free from bromine. All solutions were carefully filtered to remove suspended dust particles before their Raman spectra were measured.

Solvents and Extractions.—Diethyl ether was purified and freed from peroxides as described by Weissberger and Proskauer (" Organic Solvents," Oxford, 1935). The *iso*butyl methyl ketone used was kindly supplied by Dr. Rossotti and had been purified as described by Irving and Rossotti (*loc. cit.*). Each aqueous solution was extracted by shaking it with an approximately equal volume of organic solvent at room temperature.

Chemical Analyses.—For the analysis of the ethereal extracts, the sample was first added to excess of water and the ether removed by warming. Because of its lower volatility, *iso*butyl methyl ketone could not be removed in this way, and so ketonic extracts were exhaustively extracted with successive quantities of water. In the aqueous solutions so obtained bromine and indium were determined gravimetrically, the former as silver salt and the latter as oxide (Moser and Siegmann, *Sitzungsber. Akad. Wiss. Wien*, 1929, **139**, 612). A check on these analyses was obtained by titration of measured samples with 0·1N-sodium hydroxide solution (phenol-red as indicator). The value of [H] + 3[In] thus obtained was found to be satisfactorily in agreement with [Br].

Raman Spectra.—The Raman apparatus was that previously used by George, Rolfe, and Woodward (*loc. cit.*). The spectra were excited by a mercury-arc lamp with water-cooled electrodes (" Toronto " arc). The volume of the Raman tube was about 16 ml. For each solution a number of spectra were photographed with different exposure times up to 5 hr. on Kodak Special Scientific plates (emulsion type Oa, sensitivity G). The dispersion of the instrument is about 30 Å per mm. in the region of the lines excited by Hg 4358 Å. Frequencies were determined in the usual manner, a copper arc spectrum being used as standard. The limits of error of the $\Delta\nu$ values are $\pm$ 2 cm.$^{-1}$. The determinations of states of polarization were made with a photoelectric recording Raman spectrograph. This instrument is a much improved version of that described by Miller, Long, Woodward, and Thompson (*Proc. Roy. Soc.*, 1949, **62**, *A*, 401); a full account of it is to be published in the near future.

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The Inorganic Chemistry Laboratory,
South Parks Road, Oxford.

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The Kinetics of the Anodic Processes at Very Low Current Density. Part I. The Anodic Dissolution of Copper and Mercury.*

By S. E. S. El Wakkad, T. M. Salem, and S. E. Khalafalla.

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A new approach to the kinetics of anodic processes is made by deducing an equation expressing the potential of an electrode dissolving at a very low anodic current in terms of the rate of the electrode reaction and the gradient of the potential-determining ions at the electrode surface. The equation has been applied to the anodic dissolution of copper, and the results of the rate constant for this process so obtained are compared with those obtained with small alternating potential. The measurements have been extended to the anodic dissolution of mercury, and the rate constant of this reaction is given.

In spite of recent advances in the study of electrode processes, little is known concerning the kinetics of the anodic processes. Generally, in any electrode process three factors can be considered to control the speed of the process, *viz.*, the rate of the electrode process itself, the rate of diffusion, and the ohmic resistance of the electrolyte (Bowden and Agar, *Proc. Roy. Soc.*, **1938**, *A*, **169**, 206). Most of the previous work on electrode processes was on reactions in which the rate of the electrode process itself is very slow and thus the other two factors were neglected. Very few investigations of moderately rapid electrode processes have been made, and diffusion control has been either disregarded or minimised (Erdey-Grúz and Volmer, *Z. physikal. Chem.*, **1931**, **157**, 165; Roiter, Polnyan, and Juza, *Acta Physicochim.*, **1939**, **10**, 389, 845; Essin, *ibid.*, 1942, **16**, 102; Bonnemay, *J. Chim. phys.*, **1944**, **41**, 218). Randles (*Discuss. Faraday Soc.*, 1947, **1**, 11; *Trans. Faraday Soc.*, 1952, **48**, 828) and Randles and Somerton (*ibid.*, p. 937) measured the rates of some rapid electrode reactions at the dropping-mercury electrode upon which an alternating potential of small amplitude was applied. The reactions studied were redox reactions of the type $M^{4+} + e = M^{3+}$, and the deposition of metal ions into dilute amalgams. The electrode reactions which can be studied by this technique are limited owing to the tendency of many ions to oxidise the mercury. Hillson (*ibid.*, 1954, **50**, 385) modified Randles's theoretical treatment to suit solid electrodes when a small alternating potential is superimposed on them. Hillson applied this procedure to the reaction at a $Cu–Cu^{2+}$ electrode.

In this paper a new approach to the kinetics of anodic processes is made by deducing an equation expressing the potential of an electrode dissolving at a very low anodic current in terms of the rate of the electrode reaction and the gradient of the potential-determining ions at the electrode surface. The equation has been applied to the anodic dissolution of copper and the results of the rate constant for the dissolution of copper as obtained by our procedure are compared with those obtained with small alternating potential. The measurements have been extended to the anodic dissolution of mercury and the rate constant of such reaction is given.

The Theory of the Method.—The rate of dissolution is assumed to depend on the electrode potential according to the equation

$$\partial n/\partial t = Ake^{\alpha VzF/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n represents the number of ions dissolving in time t, A the area of the electrode, k the rate constant of the electrode process, α the fraction of the extra potential helping the dissolution process, and V the difference between the electrode potential E and the standard electrode potential E_0.

If t represents the time in seconds counted from the moment at which electrolysis has started, then it/zF would represent the number of moles of ions dissolved in time t, i being the constant current passing and zF the charge per mole of ions. When the solution is originally free from the dissolving ions and contains a sufficient amount of an indifferent

salt, the dissolving ions will diffuse away from the electrode surface. The differential equation describing this situation is $\partial c/\partial t = D(\partial^2 c/\partial x^2)$ subject to the initial condition $c = 0$ when $t = 0$, $x > 0$ and the boundary condition $c = it/zFA\delta$, when $x = 0$, $t > 0$, where δ is the thickness of a monolayer of ions, and D the diffusion coefficient of the dissolving ions. The solution of this equation is given by Carslow and Jaeger (" Conduction of Heat in Solids," Oxford, 1947, p. 45) :

$$c_{x,t} = \frac{it}{zFA\delta}\left\{\left(1 + \frac{x^2}{2Dt}\right)\operatorname{erfc}\frac{x}{2\sqrt{Dt}} - \frac{x}{\sqrt{\pi Dt}}\,e^{-x^2/4Dt}\right\} \quad . \quad . \quad . \quad (2)$$

where x is the distance from the electrode surface, and erfc the complementary to the error function defined by

$$\operatorname{erfc} y = 1 - \operatorname{erf} y = 1 - \frac{2}{\sqrt{\pi}}\int_0^y e^{-\mu^2}d\mu$$

Differentiating (2) with respect to x and setting $x = 0$, one obtains

$$\left(\frac{\partial c}{\partial x}\right)_{x=0} = -\frac{it}{zFA\delta}\frac{2}{\sqrt{\pi Dt}}$$

The rate of diffusion as given by Fick's first law would be

$$\frac{\partial n}{\partial t} = -D\left(\frac{\partial c}{\partial x}\right)_{x=0} = \frac{2i}{zFA\delta\sqrt{\pi}}\sqrt{Dt} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

At equilibrium, the rate of dissolution per unit area given by (1) must be equal to the rate of diffusion from the electrode surface given by (3); hence

$$ka_s\,e^{\alpha VzF/RT} = \frac{2i}{zFA\delta\sqrt{\pi}}\sqrt{Dt}$$

$$\therefore V = \frac{RT}{\alpha zF}\ln i + \frac{RT}{2\alpha zF}\ln t + \frac{RT}{\alpha zF}\ln\frac{2D^{\frac{1}{2}}}{zF\delta Aka_s\sqrt{\pi}} \quad . \quad . \quad . \quad . \quad (4)$$

This equation shows that the potential at the equilibrium state changes with time according to log t. This is a state of transient equilibrium slowly drifting with time. The factors which influence the value of V, as seen from equation (4), are i, k, and t, since all the other terms including D are constant for the same metal.

The plot of V against log i at corresponding times and at constant temperature should give a straight line, the slope of which is $2{\cdot}303RT/\alpha zF$ or $0{\cdot}060/\alpha z$ at 30°, from which α can be obtained and which makes an intercept with the V axis (where log $i = 0$) of $(0{\cdot}060/\alpha z) \times \log 2D^{\frac{1}{2}}/zFAka_s\delta\sqrt{\pi}$; this enables the rate constant to be calculated. Again, the plot of V against log t should be linear with a slope of $2{\cdot}303RT/2\alpha zF = 0{\cdot}060/2\alpha n$ at 30°. This treatment is valid at very low current densities, where linear diffusion due to concentration gradient is expected to occur for a measurable time.

Experimental

The electrical circuit used in determining the potential of the electrode as it is dissolved anodically at very low current density incorporated a pentode valve as a constant-current device, so the current passing was largely independent of changes in the back e.m.f. of the electrode system. The current was supplied from 120-v dry battery. The electrolytic cell was of Pyrex glass of *ca.* 150 ml. capacity. It was fitted with a rubber bung having five openings; for the anode, the syphon for the reference saturated calomel electrode, an accurate thermometer, the cathodic compartment, and an outlet for the nitrogen which was introduced through a side opening.

The copper anode was prepared by electrodeposition from an acidified copper sulphate solution with a current of 4·0 mA per electrode for 10 min. on a platinum foil one face of which was covered with soda glass, thus exposing area of 0·21 cm.². The electrode was washed several

times in conductivity water and then introduced directly into the electrolytic cell. Each experiment was carried out with a freshly prepared electrode.

The mercury anode was in the form of a circular disc of diameter 0·32 cm. and thus with an area of 0·080 cm.^{2}. This was prepared by introducing twice-distilled mercury in a cup provided with a platinum contact. The cathode was always a platinum spiral placed in its compartment in such a manner as to ensure uniform distribution of the polarising current at the anode surface.

The design of our cells, as shown before, led the more dense solution to the side of the less dense in the case of the copper electrode. In the case of mercury the denser part was below the solution. In both cases convection diffusion due to density gradients is not liable to occur in the early stages of the process. Comparison of the geometry of the diffusion processes shows that it is more difficult in the case of mercury (where the denser part was below the solution) to get convection diffusion than in the case of copper; accordingly, while constant potential was reached at about 3 min. with copper, it was not until 15 min. with mercury.

Measurements have been carried out in 0·1M-perchloric acid, and so the sole anodic process in such solution will be the dissolution of the metal (El Wakkad and Emara, *J.*, 1952, **461**; El Wakkad and Salem, *J. Phys. Chem.*, 1952, **56**, 621). The solution in the cell was boiled before use and cooled in an atmosphere of pure nitrogen to remove dissolved oxygen.

FIG. 1.

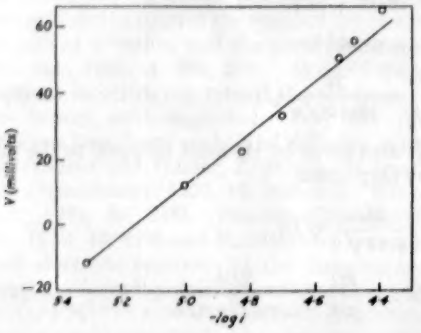
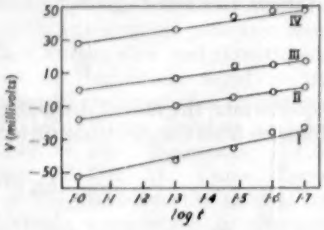


FIG. 2.



I, 5 μA. II, 10 μA.
III, 20 μA. IV, 30 μA.

Before starting each experiment the electrode was washed with conductivity water and dipped in the solution while a cathodic current was imposed on it. The cathodic polarisation was continued until a constant potential was recorded so as to ensure the reduction of any oxide present on the surface of the electrode during its preparation. The current was then adjusted to the required value, and reversed to start the anodic polarisation, and then the potential of the anode was recorded as a function of time.

All experiments, except when otherwise stated, were carried out in a water thermostat kept at 30° ± 0·1°. The reference half-cell was a saturated calomel electrode. The e.m.f. was measured with a valve potentiometer (Cambridge Instruments, England). Great care was taken to prevent the electrolytic cell from mechanical disturbances during measurements.

Results and Discussion.—Fig. 1 shows the plot of V at 1 min. against log i, for our copper electrode. The line has a slope of 0·078 which gives a value for α of 0·38. Hillson (*loc. cit.*) found $\alpha = ca.$ 1/3 for his copper electrode. The intercept with the V axis in Fig 1 has a value of $0{\cdot}402_5$. Using equation (4), one obtains

$$\frac{RT}{2\alpha zF}\ln t + \frac{RT}{\alpha zF}\ln\frac{2D^{\frac{1}{2}}}{zFAk\delta a_s\sqrt{\pi}} = 0{\cdot}402_5$$

Using a value for the diffusion coefficient of Cu^{++} of $7{\cdot}2 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ (Kolthoff and Lingane, "Polarography," Interscience, 1948, p. 45) and δ the thickness of a monolayer of Cu^{++} as 10^{-7} cm., we calculate k for the copper electrode to be $3{\cdot}6 \times 10^{-2}$ cm. sec.$^{-1}$. Randles and Somerton (*loc. cit.*) found $4{\cdot}5 \times 10^{-2}$ cm. sec.$^{-1}$ for M/1000-Cu^{++} in M-potassium nitrate.

Fig. 2 shows the plots of V against log t at different current densities: they are nearly parallel straight lines, as expected from the theory. The average slope of these lines is 0·039. The expected slope from the deduced equation is $2{\cdot}303RT/2\alpha zF$, which should be half of the slope of the V–log i straight line. The slope of the V–log i curve (Fig. 1) is 0·078 and accordingly the slope of the V–log t curve should be 0·039, which is in good agreement with the results represented in Fig. 2.

The intercept for the curve at 5 μA is found to be −0·092, and using equation (4) we have

$$-0{\cdot}092 = \frac{RT}{\alpha zF} \ln \frac{2iD^{\frac{1}{2}}}{zFAk\delta a_s\sqrt{\pi}}$$

This gives a value for k of $4{\cdot}52 \times 10^{-2}$ cm. sec.$^{-1}$ in good agreement with the value obtained from the V–log i curve.

Fig. 3 gives the plot of V against log i for the mercury anode at 30°; V was measured at 15 min. The slope of the line obtained is 0·037, which gives a value of 0·8 for α in the

FIG. 3.

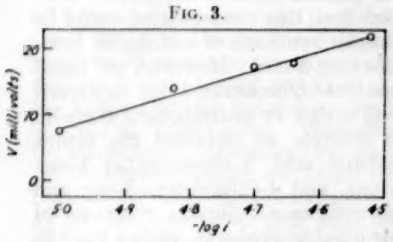
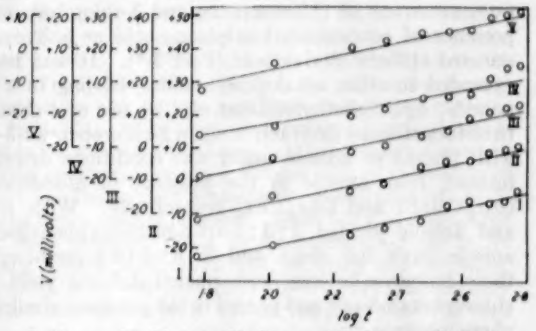


FIG. 4.



I, 10 μA. II, 15 μA. III, 20 μA. IV, 23 μA. V, 30 μA.

anodic dissolution of mercury. This line makes an intercept of 0·194 with the V axis. Applying equation (4) and using a value for the diffusion coefficient of Hg_2^{++} of $9{\cdot}2 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ (Kolthoff and Lingane, *op. cit.*, p. 258), we obtain a value for k = 0·476 cm. sec.$^{-1}$.

Fig. 4 shows the plot of V against log t at different current densities: it is a series of straight lines with an average slope of 0·021. The rate constant k can be also determined from the V–log t curves with the help of equation (4). Thus the intercept of the curve at 10 μA with the V axis has a value of −0·053, and by using equation (4) a value for k of 0·391 cm. sec.$^{-1}$ was obtained, in reasonable agreement with the results obtained from the V–log i curve.

From the above discussion it is clear that our new approach for the kinetics of anodic processes is in harmony with the results obtained experimentally. Thus the derived equation predicts a linear relation between V and log i when V is measured at the same time, and also a linear relation between V and log t at constant current i and temperature. This has been found experimentally for the dissolution of copper and mercury. From the slope and intercept of the curves we obtained for copper $\alpha = 0{\cdot}38$ and $k = 3{\cdot}6 \times 10^{-2}$ cm. sec.$^{-1}$, and for mercury $\alpha = 0{\cdot}8$ and $k = 0{\cdot}476$ cm. sec.$^{-1}$.

CAIRO UNIVERSITY, CAIRO, EGYPT. [*Received, November 10th*, 1954.]

Reactions of α-Halogeno-ketones with Aromatic Compounds. Part II. Reactions of 2-Chloropentan-3-one, 4-Chlorohexan-3-one, and s-Dichloroacetone with Phenol and its Ethers.*

By S. Husain Zaheer, Baldev Singh, Bharat Bhushan, I. K. Kacker, K. Ramachandran, and N. Shanmukha Rao.

[Reprint Order No. 6011.]

Condensation of 2-chloropentan-3-one and 4-chlorohexan-3-one with anisole in the presence of sulphuric acid or aluminium chloride yielded the triaryl-pentane and -hexane respectively, and compounds of the type $CAr_2{:}CAlk_2$, but no stilbene derivatives. *s*-Dichloroacetone condensed with phenol and its ethers to yield 1 : 3-dichloro-2 : 2-di-*p*-hydroxyphenylpropane and the corresponding ethers. With aluminium chloride resins resulted. None of these products had marked insecticidal action.

Condensation of chloroacetone and 3-chlorobutanone with phenol and its ethers in the presence of concentrated sulphuric acid or anhydrous aluminium chloride, yielded substituted stilbene derivatives (Part I *). It was hoped that this condensation could be extended to other α-halogeno-ketones, leading to a simpler synthesis of œstrogenic compounds, *e.g.*, "diethylstilbœstrol," by use of 4-chlorohexane-3-one. However, we failed to obtain stilbene derivatives when 2-chloropentan-3-one or 4-chlorohexan-3-one condensed with phenol or anisole under the conditions described earlier or modifications thereof: instead, from anisole in the presence of aluminium chloride we obtained the olefins $CAr_2{:}CMeEt$ and $CAr_2{:}CEt_2$ respectively. With sulphuric acid, 2-chloropentan-3-one and anisole yielded 2 : 3 : 3-tri-*p*-methoxyphenylpentane, and 4-chlorohexan-3-one and anisole gave the olefin and 3 : 3 : 4-tri-*p*-methoxyphenylhexane. Similar reactions of these halogeno-ketones with phenol did not yield identifiable products, except that 2-chloropentan-3-one and phenol in the presence of sulphuric acid gave 2 : 3 : 3-tri-*p*-hydroxyphenylpentane.

It appears that in the above condensations the initial reaction at the carbonyl group (Sastri, Shanmukha Rao, and Zaheer, *Current Sci.*, 1953, **22**, 338) is followed by a rearrangement involving the migration of an alkyl group (instead of one of the aromatic nuclei) leading to compounds $CAr_2{:}CAlk_2$, and/or the reaction involves, in addition to the initial condensation of two aromatic nuclei at the carbonyl group, replacement of the chlorine on the adjacent carbon atom by another aromatic residue, leading to the triaryl products.

Similar condensations employing *s*-dichloroacetone were attempted as it was hoped that insecticidal compounds might be obtained. Bakeslar reported (U.S.P. 2,455,643/1948) the condensation of ketones or halogeno-ketones with arylalkyl compounds containing at least one nuclear hydrogen atom (*e.g.*, toluene, benzyl chloride) in the presence of sulphuric or phosphoric acids at 20—40°. Pinkston found (U.S.P. 2,551,050/1951) that *s*-dichloroacetone and ethylene dichloride react with aromatic hydrocarbons having at least two replaceable nuclear hydrogen atoms, in the presence of Friedel–Crafts catalysts at 60—115°, yielding resins. In our experiments, chlorobenzene did not react with *s*-dichloroacetone in presence of concentrated sulphuric acid at 0° or at room temperature (29°). Condensation with phenol at 0—5° yielded 1 : 3-dichloro-2 : 2-di-*p*-hydroxyphenylpropane, and anisole and phenetole similarly gave 1 : 3-dichloro-2 : 2-di-*p*-methoxy- and -di-*p*-ethoxy-phenylpropane respectively. In the presence of anhydrous aluminium chloride, in place of sulphuric acid, *s*-dichloroacetone gave only resins.

None of these compounds showed marked insecticidal action against *Bruchus chinensis*, L.

During the identification of these products, it was found that, although 4 : 4'-dimethoxy-α-methylstilbene and 2 : 3-di-*p*-methoxyphenylbut-2-ene on oxidation with permanganate

* Part I, *J.*, 1954, 3360.

yielded, as expected, *p*-anisic acid and *p*-methoxyphenyl methyl ketone respectively, both yielded in addition di-*p*-methoxyphenyl ketone on oxidation with chromic acid in acetic acid. This may be explained on the assumption that an epoxide is first formed (Byers and Hickinbottom, *J.*, 1948, 1334; Hickinbottom and Wood, *Nature*, 1951, **168**, 34), yielding a glycol on hydration, which by a pinacole-pinacolone type rearrangement, followed by further oxidation gives the ketone :

$$\mathrm{CArMe{:}CArR} \longrightarrow \mathrm{ArMeC(O)CArR} \longrightarrow \mathrm{HO{\cdot}CArMe{\cdot}CArR{\cdot}OH}$$

$$\longrightarrow \mathrm{Me{\cdot}CO{\cdot}CRAr_2} \qquad \mathrm{Ar_2CO} \qquad (\mathrm{Ar} = p\text{-}\mathrm{MeO{\cdot}C_6H_4};\ \mathrm{R} = \mathrm{H\ or\ Me.})$$

Compounds of the type $CAr_2{:}CAlk_2$ gave di-*p*-methoxyphenyl ketone on oxidation with either permanganate or chromic acid.

Experimental

Phenol, anisole, and phenetole were freshly distilled before use.

4-Chlorohexan-3-one.—Attempts to prepare this compound from 4-hydroxyhexan-3-one and thionyl chloride proved unsuccessful. α-Chloro-*n*-butyryl chloride and diethylcadmium gave very poor yields of the desired compound (b. p. 50—54°/17 mm.), the major product being a liquid, b. p. 105—108°/17 mm. The chlorohexanone was obtained by chlorination of hexan-3-one, which was prepared by treating *n*-butyryl chloride with diethylcadmium (yield 46%; cf. Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518) or, more conveniently, pyrolysis of an equimolar mixture of propionic and butyric acid with manganous oxide as catalyst (Cowan, Jeffrey, and Vogel, *J.*, 1940, 171). A mixture of chlorine and carbon dioxide was bubbled through hexan-3-one, cooled in ice, the exit gases being bubbled through a weighed quantity of distilled water. When the total increase in weight was about 65% of the weight of the ketone taken, chlorination was stopped, and the product washed with water, dried (Na_2SO_4), and fractionally distilled in a Griener column under reduced pressure. From 340 g. of chlorinated hexan-3-one, after three fractionations, were obtained 193 g. of 4-chlorohexan-3-one (b. p. 49°/15 mm., 152·5—153°/712 mm.) (Blaise, *Compt. rend.*, 1912, **155**, 49, gives 53·5°/17 mm.), 40 g. of hexan-3-one, 35 g. of a chloro-ketone (b. p. 61—65°/15 mm., 170—172°/712 mm., possibly 2-chlorohexan-3-one), and 28 g. of another chloro-ketone (b. p. 72—75°/15 mm., 182—184°/712 mm.). 4-Chlorohexan-3-one was identified by oxidation with nitric acid (Van Raymenant, *Bull. Acad. roy. Belg.*, 1900, 724) to α-chlorobutyric acid, b. p. 100—102°/15 mm., d_4^{25} 1·19, n_D^{25} 1·439 (*p*-toluidide, m. p. 98°). The following derivatives of 4-chlorohexan-3-one were prepared : 2 : 4-dinitrophenylhydrazone, m. p. 64—65°; 2 : 4-dinitrophenylosazone, m. p. 259—260°; semicarbazone, m. p. 254°; phenylosazone, m. p. 137°.

Reaction of 2-Chloropentan-3-one and Anisole.—(*a*) Concentrated sulphuric acid (9·8 g., 0·1 mole) was added dropwise during 1 hr. to a stirred mixture of anisole (8·7 g., 0·08 mole) and 2-chloropentan-3-one (5 g., 0·04 mole) at 0°, stirring being continued for a further 5 hr. The red mass was kept overnight at 5—10°, treated with ice-cold water, and taken up in ether. The extract was washed with water, dilute sodium hydrogen carbonate solution, and again with water, then dried (Na_2SO_4), and the ether removed. The residue was distilled, unchanged reactants coming over first (5·2 g., b. p. 40—44°/2 mm.), followed by 2 : 3 : 3-*tri*-p-*methoxyphenylpentane* (4·2 g.), b. p. 160—180°/2 mm., which partly solidified. After two crystallisations from light petroleum, this had m. p. 142—143° (Found : C, 80·2; H, 6·7. $C_{26}H_{30}O_3$ requires C, 80·0; H, 7·7%).

(*b*) A cooled mixture of anisole (8·7 g.) and 2-chloropentan-3-one (5 g.) was added dropwise in 1 hr. with stirring to anhydrous aluminium chloride (10·7 g., 0·08 mole) cooled in an ice-bath. A dark red mass gradually becoming viscous was formed as stirring was continued for another 5 hr. Crushed ice and dilute hydrochloric acid were then added, followed by ether. The ether extract was washed with dilute hydrochloric acid, then dilute sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The solvent was distilled off and the residue (11·4 g.) distilled, yielding unchanged starting material (2·25 g.), 1 : 1-di-*p*-methoxyphenyl-2-methylbut-1-ene as a pale yellow oil (5·7 g.; b. p. 168—172°/2 mm.), and a residue (2·4 g.). During several months at 0° the oil partly crystallised. After two crystallisations from alcohol, it had m. p. 83—84° (Found : C, 80·8; H, 7·9. Calc. for $C_{19}H_{22}O_2$: C, 80·9; H, 7·8%). On oxidation with permanganate or chromic acid in acetic acid, it yielded di-*p*-methoxyphenyl ketone, m. p. and mixed m. p. 144—145° (2 : 4-dinitrophenylhydrazone, m. p. 185—187°).

Reaction of 2-*Chloropentan*-3-*one with Phenol.*—2-Chloropentan-3-one (5 g., 0·04 mole) and phenol (7·5 g., 0·08 mole) in concentrated sulphuric acid (9·8 g., 0·1 mole) at 0° gave a red viscous mass. After 5 hr. this was treated with ice and extracted with ether. The ether extract, washed with dilute sodium hydrogen carbonate solution and water, was dried (Na_2SO_4) and the ether removed. The residue was methylated with methyl sulphate and sodium hydroxide and the product (5·3 g.) was distilled, giving anisole (2 g.) followed by a fraction (2·5 g.), b. p. 140—200°/2 mm. This gradually deposited crystals, which after two crystallisations from alcohol had m. p. 141—142° alone or mixed with 2 : 3 : 3-tri-*p*-methoxyphenylpentane.

Reaction at room temperature gave a similar result.

Reaction of 4-*Chlorohexan*-3-*one with Anisole.*—(*a*) Concentrated sulphuric acid (14·7 g., 0·15 mole), anisole (10·8 g., 0·1 mole), and 4-chlorohexan-3-one (6·8 g., 0·05 mole) at 0°, reacting as in (*a*) above, gave unchanged reactants (8 g.; b. p. 42—43°/2 mm.), and an oil (3·5 g.; b. p. 170—180°/2 mm.), which deposited colourless needles (0·3 g.) of 3 : 3 : 4-*tri*-p-*methoxyphenylhexane*. Crystallised twice from light petroleum this had m. p. 142—143° (Found: C, 80·1; H, 7·1. $C_{27}H_{32}O_3$ requires C, 80·2; H, 7·9%). The rest of the distillate on prolonged storage in the refrigerator slowly deposited crystals (0·8 g.) of 2-ethyl-1 : 1-di-*p*-methoxyphenylbut-1-ene, m. p. 87—89° (cf. *J.*, 1940, 833) (Found: C, 81·2; H, 8·2. Calc. for $C_{20}H_{24}O_2$: C, 81·1; H, 8·1%). This compound on oxidation with permanganate or chromic acid yielded di-*p*-methoxyphenyl ketone.

(*b*) A cooled mixture of anisole (16·2 g., 0·15 mole) and 4-chlorohexan-3-one (10·2 g., 0·075 mole) was added dropwise in 30 min. with stirring to anhydrous aluminium chloride (20 g., 0·15 mole) cooled in ice. After 3 hr. the dark red mass became too viscous for further stirring. It was kept for 8 hr. in ice and then decomposed with crushed ice and dilute hydrochloric acid and extracted with ether. Working up as above gave unchanged reactants (2 g.; b. p. 40—44°/2 mm.), an oil (12·6 g.; b. p. 160—180°/2 mm.), and a residue (7·2 g.). The oil during 4 days in a refrigerator with a little light petroleum deposited crystals (4·5g.) of the olefin which after two crystallisations from light petroleum had m. p. and mixed m. p. 87—89°.

Reaction of s-*Dichloroacetone and Phenol.*—Concentrated sulphuric acid (9·8 g., 0·1 mole) was added dropwise during 45 min. to a stirred mixture of phenol (9·4 g., 0·1 mole) and *s*-dichloroacetone (6·35 g., 0·05 mole) cooled in ice, the stirring being continued for a further 1 hr. A red solid mass was obtained. Crushed ice was then added, followed by ether. The ether extract was washed with dilute sodium hydrogen carbonate solution and water, and dried (Na_2SO_4), and ether removed. The residue was dissolved in benzene and kept overnight in the refrigerator. Light pink needles of 1 : 3-*dichloro*-2 : 2-*di*-p-*hydroxyphenylpropane* were obtained (13·2 g., 88·9%). Recrystallised from benzene, it showed no definite m. p. but darkened at 120° (Found: C, 61·0; H, 4·9; Cl, 22·9. $C_{15}H_{14}O_2Cl_2$ requires C, 60·6; H, 4·7; Cl, 23·9%). The *diacetate*, prepared by acetic anhydride in pyridine and recrystallised from alcohol, formed colourless needles, m. p. 149—150°. The *ditoluene*-p-*sulphonate*, prepared and recrystallised similarly, formed colourless plates, m. p. 118—119° (Found: C, 56·7; H, 4·3; Cl, 11·7; S, 10·4. $C_{29}H_{26}O_6Cl_2S_2$ requires C, 57·5; H, 4·3; Cl, 11·7; S, 10·6%).

The reactions of s-dichloroacetone with anisole and phenetole under similar conditions yielded 1 : 3-*dichloro*-2 : 2-*di*-p-*methoxyphenyl*-, m. p. 58—59° (Found: C, 62·9; H, 5·7; Cl, 22·4; OMe, 17·8. $C_{17}H_{18}O_2Cl_2$ requires C, 62·8; H, 5·5; Cl, 21·8; 2OMe, 19·1%), and -*di*-p-*ethoxyphenyl-propane*, m. p. 70—71° (Found: C, 64·5; H, 6·2; Cl, 21·1; OEt, 23·1. $C_{19}H_{22}O_2Cl_2$ requires C, 64·6; H, 6·2; Cl, 20·1; 2OEt, 25·5%).

Oxidation of 4 : 4′-*Dimethoxy*-α-*methylstilbene.*—(*a*) Potassium permanganate (1 g. in 25 ml. of water) and acetic acid (1 ml.) were added to 4 : 4′-dimethoxy-α-methylstilbene (0·5 g.), and the contents stirred for 1 hr. Excess of permanganate was decomposed ($NaHSO_3$) and from the filtrate anisic acid, m. p. 182—184°, was isolated by the usual methods.

(*b*) Chromic acid (4 g.), glacial acetic acid (20 ml.), and 4 : 4′-dimethoxy-α-methylstilbene (1 g.) were refluxed for 30 min. To the cooled mixture diluted with water, alkali was added to neutrality, followed by ether. The ether extract yielded di-*p*-methoxyphenyl ketone, m. p. and mixed m. p. 144—145°. The aqueous layer on acidification and ether extraction yielded anisic acid.

Oxidation of 2 : 3-*Di*-p-*methoxyphenylbut*-2-*ene.*—(*a*) The butene (0·5 g.) in acetone (25 ml.) was mixed with potassium permanganate (0·8 g. in 10 ml. water) and acetic acid (1 ml.). After 3 hr. the excess of permanganate was decompsed ($NaHSO_3$) and the filtrate made alkaline and extracted with ether. The ether extract yielded *p*-methoxyacetophenone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 219—220°).

(*b*) Chromic acid (2 g.), glacial acetic acid (10 ml.), and the butene (0·5 g.) were refluxed for 30 min. Anisic acid, m. p. 180°, and the ketone, m. p. 144—145°, were obtained.

The authors acknowledge some preliminary work done by Dr. P. M. Bhargava. They are grateful to Dr. M. B. Naidu for carrying out the insecticidal tests.

CENTRAL LABORATORIES FOR SCIENTIFIC AND INDUSTRIAL RESEARCH,
HYDERABAD-DECCAN, 7, INDIA. [*Received, partly, December 14th*, 1954; *partly, January 4th*, 1955.]

The Degradation of Carbohydrates by Alkali. Part X. Acetal Derivatives.*

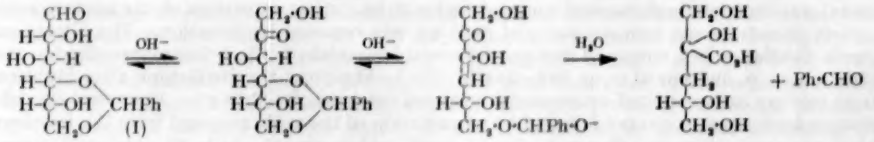
By W. M. CORBETT, J. KENNER, and G. N. RICHARDS.

[Reprint Order No. 6071.]

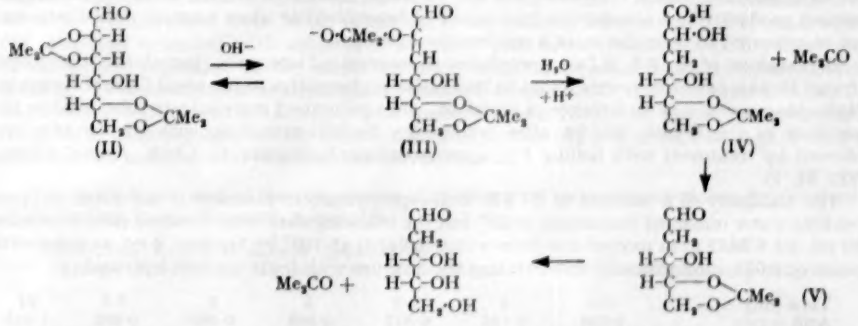
4 : 6-*O*-Benzylidene-D-glucose and 2 : 3-5 : 6-di-*O*-*iso*propylidene-D-mannose furnish D-gluco*iso*saccharinic and a mixture of 5 : 6-*iso*propylidene-D-*meta*-saccharinic acids respectively on treatment with lime-water.

IT has hitherto been accepted that groupings of the acetal type are stable towards alkali, but their relation to alkoxy-groupings suggests that lability should be conferred by the presence of a carbonyl group in the β-position relative to one of the acetal oxygen atoms. The two compounds we have now studied in this respect are representative of the two types in this category which must be distinguished, according as the second acetal oxygen atom is closer to, or more remote from, the carbonyl group than the first.

Thus **4 : 6-*O*-benzylidene-D-glucose** (I) is smoothly converted by lime-water at 25° into a mixture of α- and β-D-gluco*iso*saccharinic acids and benzaldehyde :



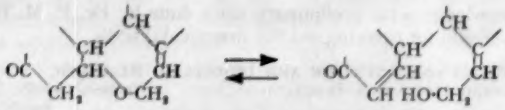
2 : 3-5 : 6-Di-*O*-*iso*propylidene-D-mannose (II) does not exhibit the same facility of decomposition because the anion (III) initially formed cannot at once pass into an α-diketone and thence into a saccharinic acid so that the reversibility of the initial reaction operates. However, dissociation occurs at 100°, yielding 3-deoxy-5 : 6-*iso*propylidene-D-gluconic and -mannonic acid (IV) and acetone.



The limited formation of *iso*strychnine from strychnine in water at 170° or methyl alcoholic ammonia at 140° (Bacovescue and Pictet, *Ber.*, 1905, **38**, 2787; Leuchs and

* Part IX, *J.*, 1955, 1431.

Nitschke, *ibid.*, 1922, **55**, 3171) by opening of the latter's F-ring appears to be a reaction closely analogous to the present :



In this instance separation of the alcoholic from the αβ-unsaturated carbonyl grouping is impossible and an equilibrium must ensue which is however affected by the energy content of the system.

The nature of the mixed 3-deoxy*iso*propylidene-D-mannonic and -D-gluconic acids is demonstrated by hydrolysis in presence of sulphuric acid or an acidic resin to acetone and 3-deoxy-D-mannonic and -gluconic acid. Accordingly, when the calcium salts of the mixed *iso*propylidene-acids are subjected to the Ruff procedure (*Ber.*, 1901, **34**, 1362) they yield 2-deoxy-4 : 5-*iso*propylidene-D-ribose, the identity of which is demonstrated by hydrolysis in presence of an acidic resin. Acetone and 2-deoxy-D-ribose were thus produced, the latter being identified by paper chromatography, but the reaction is not to be regarded as a satisfactory means of preparing it. The 2-deoxy*iso*propylidene-D-ribose is also accessible by periodate oxidation of the 3-deoxy*iso*propylidene-D-mannonic–D-gluconic acid mixture, but the product is less satisfactory than that just described.

Experimental

Degradation of 4 : 6-O-*Benzylidene*-D-*glucose*.—A quantitative study of the course of the reaction with lime-water at 25° was vitiated by separation of a gelatinous precipitate and consequent unsatisfactory sampling, but the odour of benzaldehyde was perceptible after 5 min. and reaction seemed complete after 7 hr. A suspension (5·03 g.) in oxygen-free lime-water (750 ml.; 0·04N) was therefore kept at room temperature for 20 hr. After saturation of the mixture with carbon dioxide brown resinous material (0·95 g.) was removed by filtration. The filtrate on steam-distillation in a stream of nitrogen furnished benzaldehyde [2 : 4-dinitrophenylhydrazone (2·57 g.), m. p. and mixed m. p. 243—244°]. The residue from the distillation, after filtration from calcium carbonate and evaporation, furnished calcium salts (2·52 g.). Fractional crystallisation from aqueous alcohol followed by examination of the acids prepared from the fractions by paper chromatography (butanol–ethanol–acetic acid–water, 45 : 5 : 1 : 49; hydroxylamine–ferric chloride spray; Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859) showed them to be almost exclusively salts of α-*iso*saccharinic acid (lactone, R_F 0·48), with a trace of those of the β-acid (lactone, R_F 0·54). Accordingly the less soluble fractions freed from calcium ions by treatment with resin, furnished brucine α-*iso*saccharinate, m. p. and mixed m. p. 159—161°, $[\alpha]_D^{21}$ −25° (*c*, 1 in H_2O). Nef (*Annalen*, 1910, **376**, 89) gives m. p. 164°. The same brucine salt, m. p. and mixed m. p. 158—160°, was also prepared in small yield from the above-mentioned resinous product which also gave a faint odour of benzaldehyde when warmed with dilute acid and so appeared to be in the main a condensation product.

Degradation of 2 : 3-5 : 6-*Diisopropylidene*-D-*mannose*.—Dom nuts, kernels of the North African *Hyphaene thebaica*, were found to be a suitable alternative to the usual Central American *Phytelephas macrocarpa* as a source of mannose. The pulverised material was submitted to the procedure of *Org. Synth.*, **22**, 86, after preliminary Soxhlet-extraction with trichloroethylene followed by treatment with boiling 1% aqueous sodium hydroxide (cf. Clark, *J. Biol. Chem.*, 1922, **51**, 1).

The alkalinity of a solution of 2 : 3-5 : 6-di*iso*propylidene-D-mannose in saturated oxygen-free lime-water remained unchanged at 25°, but the following data were obtained from a solution (50 ml.)of 0·3453 g. in oxygen-free lime-water (0·042N) at 100° by treating 2-ml. samples with excess of 0·01N-sulphuric acid and titrating the mixture with 0·01N-sodium hydroxide :

Time (hr.)	0·5	1	2·5	4	6	7·5	24
Acid (equiv.)	0·064	0·145	0·312	0·506	0·660	0·682	1·282

The excess of acid finally observed possibly arises from condensation products of the acetone formed.

After a solution (5 l.) of di-*O*-*iso*propylidenemannose (39·12 g.) in oxygen-free lime-water

(0·044N) had been kept for 41 hr. at 100° and cooled, excess of carbon dioxide was added and the mixture boiled and filtered. Acetone 2 : 4-dinitrophenylhydrazone (0·183 g.; m. p. and mixed m. p. 123—125°) was prepared from the first 25 ml. of the distillate from 100 ml. of filtrate. The remainder, when evaporated and extracted with acetone, yielded calcium salts (35·90 g.). By use of this material, (*a*) an aqueous solution (20 ml.) of 4·696 g., treated with acetone (30 ml.), yielded at room temperature a first fraction (1·706 g.), $[\alpha]_D^{23}$ −7·4° (*c*, 1·08 in H_2O) which after recrystallisation from aqueous acetone (2 : 3) had $[\alpha]_D^{24}$ −5·2° (*c*, 1·34 in H_2O) and on treatment with Amberlite resin IR-120(H) yielded acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 123—125°) with 3-deoxy-gluconic and -mannonic acid identified as lactones by paper chromatography (cf. *J.*, 1954, 1784). A second fraction {0·473 g.; $[\alpha]_D^{21}$ −18·8° (*c*, 0·854 in H_2O)} separated on further cooling and on recrystallisation from aqueous acetone (2 : 3) had $[\alpha]_D^{24}$ −18·2° (*c*, 1·2 in H_2O). *Calcium 3-deoxy-5 : 6-O-isopropylidenemannonate* (Found : C, 43·3; H, 6·5; Ca, 8·3. $C_{18}H_{30}O_{12}Ca,H_2O$ requires C, 43·6; H, 6·5; Ca, 8·1%) thus prepared yielded on hydrolysis with acidic resin, acetone, and 3-deoxymannonolactone, m. p. and mixed m. p. 87—89·5°; Nef (*loc. cit.*) gives m. p. 92°. Chromatographic examination did not reveal any 3-deoxygluconolactone. (*b*) An aqueous solution of 0·323 g., on treatment with Amberlite IR-120(H) resin and concentration, yielded a syrup (0·201 g.) from which a few clusters of crystals, m. p. and mixed m. p. with authentic 3-deoxygluconolactone, 97·5—99·5°. Bef (*loc. cit.*) gives m. p. 104° (*c*) A solution in dilute sulphuric acid (0·1N; 100 ml.) of 1·575 g., heated 1 hr. at 100°, yielded mixed calcium salts (1·000 g.) after neutralisation with barium carbonate, filtration, and partial distillation [the distillate (50 ml.) yielding acetone 2 : 4-dinitrophenylhydrazone (0·481 g.), m. p. and mixed m. p. 123—125°], treatment with Amberlite IR-120(H) resin, neutralisation with calcium carbonate, filtration, and concentration. From these salts by crystallisation from 33% aqueous ethanol, was obtained calcium 3-deoxymannonate (0·241 g.), $[\alpha]_D^{22}$ −22·0° (*c*, 2·41 in H_2O), further characterised by conversion into 3-deoxy-γ-D-mannonolactone (0·156 g.), m. p. and mixed m. p. (Richards, *J.*, 1954, 3638) 83—85°. Nef (*loc. cit.*) gives $[\alpha]_D$ −23·3° and m. p. 92°. (*d*) An aqueous solution (100 ml.) of 12·05 g. was treated with barium acetate (1·15 g.) and ferric sulphate (0·60 g.). The mixture was boiled for several minutes, filtered, cooled to 40°, and treated with hydrogen peroxide (30%; 7 ml.). A further equal quantity of peroxide was added when the reaction had subsided. Finally, the cooled mixture was extracted with ether (3 × 50 ml.). The total extract, when dried (Na_2SO_4) and evaporated, furnished a syrup (0·870 g.), $[\alpha]_D^{22}$ −4·6° (*c*, 0·86 in H_2O), $[\alpha]_D^{23}$ +10·2° (*c*, 0·75 in pyridine), and further material (2·230 g.) resulted from treatment of the aqueous mother-liquors with barium acetate, ferric sulphate, and hydrogen peroxide. Although chromatographic analysis (butanol–pyridine–water; 3 : 2 : 1·5) indicated its essential uniformity (R_y 0·90; trace spots R_y 0·62 and 0·49; silver nitrate, sodium hydroxide spray, Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 144) analytical data were in poor accord with those required by 2-deoxy-4 : 5-*iso*propylideneribose, and the usual crystalline derivatives could not be obtained. Traces of formaldehyde (dimedone derivative, m. p. and mixed m. p. 187·5—189·5°) were detected in the product. (*e*) Calcium ions were removed from a solution (100 ml.) of 5·058 g. by use of the calculated quantity of sodium oxalate, and the filtered solution was then treated with one of sodium metaperiodate (10 g.) and with sodium hydrogen carbonate (0·5M; 30 ml.). The mixture, after 24 hr. in the dark, was filtered, concentrated to a small volume (25 ml.), and extracted with ether (3 × 50 ml.). The extract yielded a pale yellow syrup (1·583 g.) and repetition of the whole operation with the aqueous liquor afforded a further 0·453 g. Chromatographic analysis again furnished a main spot, R_y 0·90 (impurities, R_y 0·75 and 0·66), and treatment of the syrup with Amberlite resin IR-120(H) furnished 2-deoxyribose (R_y 0·61) as main product, but the accompanying impurities (R_y 0·12, 0·23, 0·32, 0·46, 0·69, 0·78) inhibited the isolation of crystalline derivatives from it.

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THE BRITISH RAYON RESEARCH ASSOCIATION,
BARTON DOCK ROAD, URMSTON, NR. MANCHESTER. [*Received, January 26th*, 1955.]

Organometallic Compounds of the Alkali Metals. Part V. The Non-radical Decomposition of* n-*Butyl-lithium.*

By D. Bryce-Smith.

[Reprint Order No. 6120.]

Solutions of *n*-butyl-lithium in *iso*propylbenzene decompose at 135° with the evolution of butane and butene, the latter slightly predominating : 2 : 3-dimethyl-2 : 3-diphenylbutane is not formed. In contrast, photolysis both of di-*n*-butylmercury and of a mixture of *n*-butyl iodide and silver in *iso*propylbenzene leads to evolution of butane and a little butene : 2 : 3-dimethyl-2 : 3-diphenylbutane is produced in each case. From this evidence, and from earlier work, it is concluded that thermal decomposition of alkali-metal alkyls does not produce alkyl radicals.

Morton and Cluff (*J. Amer. Chem. Soc.*, 1952, **74**, 4056; 1953, **75**, 134) reported the isolation of metallic sodium on thermal decomposition of *n*-pentylsodium, and concluded that radicals are present under those conditions where *n*-pentylsodium is used : n-$C_5H_{11}Na \longrightarrow n$-$C_5H_{11}\cdot + Na$ (cf. Morton and Newey, *ibid.*, 1942, **64**, 2247). Such behaviour, while recalling that of, *e.g.*, alkyl-mercury and -lead compounds, is difficult to reconcile with various other observations. Thus, Carothers and Coffman (*ibid.*, 1929, **51**, 588) found that thermal decomposition of ethylsodium was best represented by the equation, $C_2H_5Na \longrightarrow C_2H_4 + NaH$. Sodium was produced at temperatures above 142° by dissociation of sodium hydride. Ziegler and Gellert (*Annalen*, 1950, **567**, 179) obtained broadly similar results for the thermal decomposition of ethyl- and *n*-butyl-lithium. It is, of course, well known that the thermal-decomposition stage of Tschitschibabin-type reactions involves the elimination of alkali-metal hydride. In Part III (*J.*, 1954, 1079), no evidence was found for the formation of *n*-pentyl radicals when *n*-pentylsodium was suspended in *iso*propylbenzene under conditions where appreciable thermal decomposition of the reagent must have occurred. Free *n*-pentyl radicals would have been expected to produce αα-dimethylbenzyl radicals by abstraction of hydrogen from the medium, and the latter radicals should then have dimerised to 2 : 3-dimethyl-2 : 3-diphenylbutane. No trace of the dimer was obtained from this or from similar reactions when alkylpotassium compounds were used.†

In the present work, *iso*propylbenzene was used as a detector for possible free-radical intermediates in the thermal decomposition of *n*-butyl-lithium. This comparatively non-polar lithium compound seemed to offer a better chance of homolytic dissociation than would the more polar sodium or potassium compounds. This decomposition at 135° gives no 2 : 3-dimethyl-2 : 3-diphenylbutane. In addition to the butene expected from the reaction, n-$C_4H_9Li \longrightarrow n$-$C_4H_8 + LiH$, some butane is evolved. Formation of the saturated hydrocarbon in smaller amount was observed by Ziegler and Gellert (*loc. cit.*; cf. Carothers and Coffman, *loc. cit.*) both in "dry" decompositions and in the presence of *n*-octane. They very reasonably ascribed it to metallation of the olefin : $CH_3{\cdot}CH_2{\cdot}CH{=}CH_2 + n$-$C_4H_9Li \longrightarrow CH_3{\cdot}CHLi{\cdot}CH{=}CH_2 + n$-$C_4H_{10}$. In the present case, some metallation of the solvent also occurred. The formation of butane does not imply the intermediate production of butyl radicals.

To confirm the belief that the non-formation of 2 : 3-dimethyl-2 : 3-diphenylbutane was truly diagnostic of a non-radical reaction, *n*-butyl radicals were generated in *iso*propylbenzene by two methods, (*a*) photolysis of di-*n*-butylmercury and (*b*) photolysis of a mixture of *n*-butyl iodide and silver powder. [These reactions were chosen in the belief that only one radical species would be formed : the two C–Hg bonds in dialkylmercury compounds

* *J.*, 1954, 2743 is regarded as Part IV.

† Subsequent unpublished work has shown that the Schorigin metallation procedure (*Ber.*, 1910, **43**, 1931, 1938) produces small quantities of the above dimer when carried out in *iso*propylbenzene. The free radicals evidently formed are almost certainly derived from the decomposition of an intermediate mercury compound, and not from alkali-metal alkyls.

are believed to break simultaneously (Chilton and Gowenlock, *Trans. Faraday Soc.*, **1953**, **49**, 1451; **1954**, **50**, 824)]. 2 : 3-Dimethyl-2 : 3-diphenylbutane was obtained in each case, and the gas evolved was 85—90% butane with 10—15% of butene. Decomposition of *n*-butyl iodide was very incomplete and the yield of 2 : 3-dimethyl-2 : 3-diphenylbutane was low: the yield from di-*n*-butylmercury was nearly 50%. The virtual non-formation of *n*-octane indicates that the stationary concentration of *n*-butyl radicals was much lower than that of αα-dimethylbenzyl radicals, as one would expect from their relative reactivities. Little or no fragmentation of *n*-butyl radicals was detected. Although new in their present application, these photodecompositions provide unquestionable sources of *n*-butyl radicals, and they can be extended to the production of phenyl radicals in solution (Bryce-Smith, Hey, and Pengilly, unpublished work). They confirm the view that *n*-butyl radicals are not formed during the thermal decomposition of *n*-butyl-lithium. From the results quoted in Part III (*loc. cit.*) and discussed above, a similar conclusion applies to the decomposition of alkyl-sodium and -potassium compounds. Morton and Cluff's results (*locc. cit*) are hard to understand; but their significance is put in some doubt by the apparent failure to ascertain what excess of sodium remained from the initial preparation of *n*-pentylsodium.

Experimental

Thermal Decomposition of n-*Butyl-lithium in* iso*Propylbenzene.*—A 1·71N-solution of *n*-butyl-lithium in *n*-pentane was prepared as described in Part II (*J.*, 1953, 861). *n*-Pentane was distilled under reduced pressure from 25 ml. (0·043 mole) of the clear solution and 50 ml. of dried (CaH_2), freshly refractionated *iso*propylbenzene were then added. At 135° (nitrogen atmosphere), a pale brown solid was precipitated (presumably lithium hydride) and gas was steadily evolved. After 24 hr. at 135°, the dark brown product was cooled and poured on solid carbon dioxide and ether. Addition of water produced a brisk evolution of hydrogen, but the brown colour was not discharged. Washing of the separated organic layer with water removed most of the coloured material. The combined aqueous layers were acidified and extracted with light petroleum (b. p. <40°). Removal of the solvent gave 0·02 g. of an oily colourless mixture of cuminic acids. The amount was too small for analysis by the method described in Part III (*loc. cit.*), but from the rapid reduction of warm alkaline permanganate it is likely that nuclear isomers predominated. Fractional distillation of the dried *iso*propylbenzene solution gave no octane (judged by refractive indices). The material of b. p. >180° amounted to 0·3 g. Chromatography on alumina gave 0·05 g. of an oil with an odour resembling that of the higher alkylbenzenes, but no trace of 2 : 3-dimethyl-2 : 3-diphenylbutane or other crystalline material.

The gas evolved during the thermal decomposition was found to contain *ca.* 60% of butene and 40% of butane. No lower-boiling hydrocarbons were detected.

*Photolysis of Di-*n*-butylmercury in* iso*Propylbenzene.*—A solution of di-*n*-butylmercury (6·05 g., 0·0192 mole) in dry *iso*propylbenzene (25 ml.) was irradiated with ultraviolet light under nitrogen in a quartz flask for 25 hr. at 135°. A 200-w medium-pressure mercury-vapour lamp was used at a distance of 1 cm. from the vessel: it also served as a heater, and the flask temperature was regulated by means of a current of cold air. Mercury (3·5 g., 91%) was removed by filtration. Fractional distillation and refractive-index measurements showed the presence of not more than 0·05 g. (2%) of octane. The pale yellow residue, b. p. >160°, was treated with methyl alcohol to give 1·95 g. (43% based on di-*n*-butylmercury; 47% based on mercury liberated) of 2 : 3-dimethyl-2 : 3-diphenylbutane, m. p. 117°. One recrystallisation from ethyl alcohol gave pure material, m. p. and mixed m. p. 118·5°.

The gas evolved during the photolysis was found to be a mixture of butane 85% and butene 15%, with no more than traces of lower-boiling hydrocarbons.

In a control experiment, irradiation of *iso*propylbenzene under nitrogen in the presence of mercury gave no detectable amount of 2 : 3-dimethyl-2 : 3-diphenylbutane.

Photolysis of n-*Butyl Iodide in* iso*Propylbenzene.*—Preliminary experiments showed that although iodine is rapidly liberated by the irradiation of solutions of *n*-butyl iodide in *iso*propylbenzene, decomposition soon becomes very slow, presumably owing to absorption of the radiation by iodine. Silver powder was added in order to overcome this difficulty. It reacts with iodine but is inert to *n*-butyl iodide.

A solution of *n*-butyl iodide (3·7 g., 0·02 mole) in dry *iso*propylbenzene (20 ml.) was stirred with silver powder (3·25 g., 0·03 g.-atom) and irradiated as above at 125—135° for 35 hr. under

nitrogen. Most of the *n*-butyl iodide was recovered, but 0·15 g. of 2 : 3-dimethyl-2 : 3-diphenylbutane, m. p. 116° and mixed m. p. 116·5°, was obtained. The small amount of gas which was evolved was found to be a mixture of butane *ca.* 90% and butene 10%.

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KING'S COLLEGE, LONDON, W.C.2. [*Received, February 11th,* 1955.]

1-*Phenylnaphthalenes. Part II.** *The Cyclisation of Ethyl Hydrogen γγ-Di-o-methoxyphenyl- and γγ-Di-p-methoxyphenyl-itaconate to the Corresponding* 1-*Phenylnaphthalenes.*

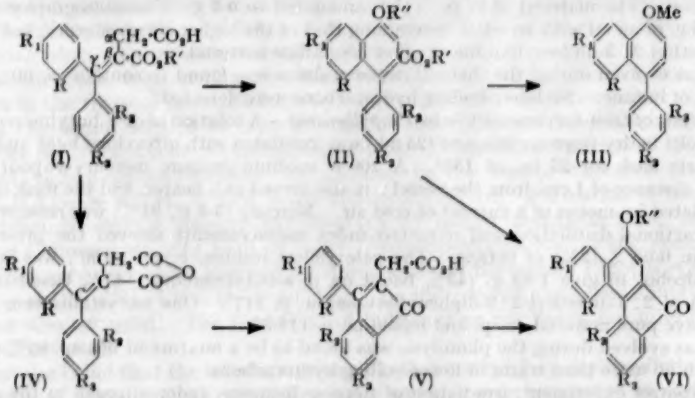
By F. G. BADDAR, LANSON S. EL-ASSAL, and (MRS.) VICTORINE B. BAGHOS.

[Reprint Order No. 5700.]

Ethyl hydrogen γγ-di-*o*- and -*p*-methoxyphenylitaconate are converted by use of acetic anhydride and sodium acetate into the corresponding 1-phenylnaphthalene derivatives.

γγ-Di-*p*-methoxyphenylitaconic anhydride yields with aluminium chloride an indenone, which is cyclised and methylated to 2 : 2′ : 7-trimethoxybenzofluorenone. However, the *o*-methoxyphenyl isomer when similarly treated gives 4-*o*-methoxyphenyl-3-coumarinylacetic acid.

SYMMETRICALLY disubstituted benzophenones were condensed with diethyl succinate, potassium *tert.*-butoxide being the catalyst (cf. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 74; 1950, **72**, 511); 2 : 2′-dimethoxybenzophenone thereby gave ethyl hydrogen γγ-di-*o*-methoxyphenylitaconate (I; R = R_2 = OMe, R_1 = R_3 = H, R′ = Et). Use of a suspension of potassium ethoxide in benzene as catalyst gave an unsatisfactory product containing di-*o*-methoxyphenylmethanol, probably formed by a Meerwein–Pondorff type of reduction (cf. Johnson *et al.*, *loc. cit.*, 1947).

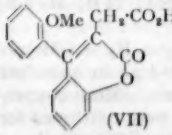


Cyclisation of the half-esters (I; R = R_2 = H, R_1 = R_3 = OMe, R′ = Et; and R = R_2 = OMe, R_1 = R_3 = H, R′ = Et) with sodium acetate in acetic anhydride (Borsche *et al.*, *Annalen*, 1936, **526**, 1) gave ethyl 4-acetoxy-6-methoxy-1-*p*-methoxyphenyl- and ethyl 4-acetoxy-8-methoxy-1-*o*-methoxyphenyl-2-naphthoic acid (II; R′ = Et, R″ = Ac; R = R_2 = H, R_1 = R_3 = OMe, and conversely). The derived phenolic acids (II; R = R_2 = R′ = R″ = H, R_1 = R_3 = OMe; and R = R_2 = OMe, R_1 = R_3 =

* Part I, *J.*, 1948, 1270.

R′ = R″ = H) were converted by methyl iodide into methyl 4 : 6-dimethoxy-1-*p*-methoxyphenyl- and 4 : 8-dimethoxy-1-*o*-methoxyphenyl-2-naphthoate, respectively. These were hydrolysed to the acids, which were decarboxylated to the corresponding 1-phenylnaphthalene derivatives.

The acid (II; R = R_2 = R′ = H, R_1 = R_3 = OMe, R″ = Me) gave, on cyclisation with phosphoric oxide, 2 : 2′ : 7-trimethoxy-3 : 4-benzofluorenone (VI; R = R_2 = H, R_1 = R_3 = OMe, R″ = Me), also obtained through the following series of reactions: γγ-Di-*p*-methoxyphenylitaconic anhydride (IV; R = R_2 = H, R_1 = R_3 = OMe) (cf. Johnson *et al.*, *loc. cit.*) was cyclised with aluminium chloride in nitrobenzene to 6-methoxy-3-*p*-methoxyphenyl-1-oxo-2-indenylacetic acid (V; R = R_2 = H, R_1 = R_3 = OMe). This keto-acid was cyclised with acetic anhydride and sodium acetate (cf. Borsche *et al.*, *loc. cit.*) to 2-acetoxy-2′ : 7-dimethoxy-3 : 4-benzofluorenone (VI; R = R_2 = H, R_1 = R_3 = OMe, R″ = Ac), which was hydrolysed and then methylated to give the above benzofluorenone. However, when γγ-di-*o*-methoxyphenylitaconic anhydride (IV; R = R_2 = OMe, R_1 = R_3 = H) was treated with aluminium chloride in nitrobenzene, it gave 4-*o*-methoxyphenyl-3-coumarinylacetic acid (VII) instead of the expected compound of type (V). The structure of (VII) was deduced from the fact that, when it was refluxed with sodium hydroxide solution and dimethyl sulphate (cf. Stoermer and Friemel, *Ber.*, 1911, **44**, 1343), it gave γγ-di-*o*-methoxyphenylitaconic acid. Its formation may be due to partial demethylation of γγ-di-*o*-methoxyphenylitaconic anhydride (IV; R = R_2 = OMe, R_1 = R_3 = H) by the aluminium chloride to (IV; R = OMe, R_2 = OH, R_1 = R_3 = H) and conversion of this into (VII) either by rearrangement, or by recyclisation of (I; R = OMe, R_2 = OH, R_1 = R_3 = R′ = H) on acidification of its solution in alkali carbonate.



(VII)

Attempted decarboxylation and lactonisation of γγ-di-*o*-methoxyphenylitaconic acid (cf. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 511) failed, possibly owing to the stabilisation of the carboxyl group in chelation with the *o*-methoxyl group.

Attempts to prepare an authentic specimen of 4 : 8-dimethoxy-1-*o*-methoxyphenylnaphthalene (III; R = R_2 = OMe, R_1 = R_3 = H) by condensation of 1 : 5-dimethoxynaphthalene and diazotised methyl 3-aminoanisate in presence of sodium hydroxide solution (cf. Baddar, *J.*, 1941, 310) were not successful. Its preparation by the condensation of *o*-iodoanisate with 1-iodo-4 : 8-dimethoxynaphthalene could not be accomplished owing to the failure to obtain a satisfactory yield of the latter compound, from the corresponding amine (cf. Thomson, Race, and Rowe, *J.*, 1947, 354), or by direct iodination (cf. Derbyshire and Waters, *J.*, 1950, 3694; Seer and Ehrenreich, *Monatsh.*, 1913, **34**, 631).

Likewise, 2 : 2′-dimethylbenzophenone (Cook, *J.*, 1930, 1091) failed to condense with diethyl succinate. However, this study is being extended to other mono- and poly-substituted benzophenones.

Experimental

2 : 2′-*Dihydroxybenzophenone.*—A finely powdered mixture of xanthone (2 g.) and potassium hydroxide (1·7 g.) was fused at 205—210° for 20 min. The product was digested with water, and the clear alkaline extract (charcoal) acidified. The precipitated 2 : 2′-dihydroxybenzophenone was filtered off, washed, and dried. On crystallisation from light petroleum (b. p. 40—60°), it was obtained in lemon-yellow crystals (1·4 g.), m. p. 62—63°. Richter (*J. pr. Chem.*, 1883, **28**, 285) and Graebe and Feer (*Ber.*, 1886, **19**, 2609) gave m. p. 59—60° (Found: C, 73·1; H, 4·4; active H, 0·65. Calc. for $C_{13}H_{10}O_3$: C, 72·9; H, 4·6; active H, 0·93%).

2 : 2′- *and* 4 : 4′-*Dimethoxybenzophenone.*—These were prepared by the methylation of the corresponding dihydroxy-compounds (21·4 g.), with methyl sulphate (50·4 g.) and potassium carbonate (55·2 g.) in acetone (200 ml.) (15 hours' refluxing). 4 : 4′-Dimethoxybenzophenone formed needles (*ca.* 29 g.) (from ethyl alcohol), m. p. 145—146° (Schnackenberg and Scholl, *Ber.*, 1903, **36**, 654, gave m. p. 144°); 2 : 2′-dimethoxybenzophenone (*ca.* 22 g.) had m. p. 104—105° (from methanol).

Ethyl 4-*Acetoxy*-6-*methoxy*-1-p-*methoxyphenyl*-2-*naphthoate* (II; R = R_2 = H, R_1 = R_3 = OMe, R′ = Et, R″ = Ac).—A mixture of crude ethyl hydrogen γγ-di-*p*-methoxyphenylitaconate (Johnson *et al.*, *loc. cit.*) (3·7 g.), sodium acetate (0·8 g.), and acetic anhydride (20 ml.)

was refluxed for 5 hr. The product was cooled, acetic anhydride decomposed, and the insoluble oil extracted with benzene. The extract was washed successively with water, sodium carbonate solution, and water, and dried ($CaCl_2$). Distillation of the solvent left a brown oily mass (*ca.* 3·2 g.), which solidified on trituration with ether. On crystallisation from acetone, the ester was obtained in aggregates, m. p. 198—199° (Found : C, 70·6; H, 5·5; OMe, 24·0. $C_{23}H_{22}O_6$ requires C, 70·1; H, 5·6; OMe, 23·6%).

4-Hydroxy-6-methoxy-1-p-methoxyphenyl-2-naphthoic Acid.—The above ester on hydrolysis with 10% alcoholic potassium hydroxide, and working up as usual, afforded the *acid* (1·8 g.) which after crystallisation from glacial acetic acid had m. p. 219—220° (shrinking at 218°) (Found : C, 69·8; H, 4·9; OMe, 21·3. $C_{19}H_{16}O_5$ requires C, 70·2; H, 4·9; OMe, 19·1%). Its *ethyl ester* after crystallisation from benzene had m. p. 199—200° (shrinking at 197°) (Found : C, 72·1; H, 5·7; OMe, 25·2. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·7; OMe 26·4%). Methylation of the foregoing acid (3·3 g.) by methyl iodide (6 ml.) and potassium carbonate (3 g.) in acetone (15 ml.) (12 hours' refluxing) afforded *methyl* **4 : 6-dimethoxy-1-p-methoxyphenyl-2-naphthoate** (3·4 g.) in aggregates, m. p. 127—128° (Found : C, 71·4; H, 5·6; OMe, 37·7. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·6; OMe, 35·2%), from benzene.

On hydrolysis with 10% alcoholic potassium hydroxide (II; R = R_2 = H, R_1 = R_3 = OMe, R′ = R″ = Me) gave the corresponding *acid*, in pale yellow flakes, m. p. 205—206° (from glacial acetic acid) (Found : C, 70·7; H, 5·3; OMe, 27·4. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3; OMe, 27·4%).

4 : 6-Dimethoxy-1-p-methoxyphenylnaphthalene (III; R = R_2 = H, R_1 = R_3 = OMe).—A stirred solution of **4 : 6**-dimethoxy-**1-*p*-**methoxyphenyl-2-naphthoic acid (0·4 g.) in quinoline (4 ml.), and copper-bronze (0·25 g.) were heated to 205—210° during 30 min. More copper-bronze (0·25 g.) was added portionwise during 2 hr., and stirring and heating were continued for a further hour. The product was worked up as usual, and then crystallised from light petroleum (b. p. 80—100°), giving **4 : 6-dimethoxy-1-p-methoxyphenylnaphthalene** in light brown aggregates (*ca.* 0·3 g.), m. p. 117·5—118·5° (shrinkage at 116°) (Found : C, 77·7; H, 6·1; OMe, 31·9. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1; OMe, 31·8%).

γγ-Di-p-methoxyphenylitaconic Acid (I; R = R_2 = R′ = H, R_1 = R_3 = OMe).—The half-ester (I; R = R_2 = H, R_1 = R_3 = OMe, R′ = Et) was hydrolysed with 10% aqueous-alcoholic potassium hydroxide solution (v/v) (2 hours' refluxing) to the acid, m. p. 161—162°.

6-Methoxy-3-p-methoxyphenyl-1-oxo-2-indenylacetic Acid (V; R = R_2 = H, R_1 = R_3 = OMe).—A finely powdered mixture of **γγ-di-*p*-**methoxyphenylitaconic anhydride (3 g.) (Johnson *et al., loc. cit.*) and aluminium chloride (1·5 g.) was gradually added to stirred and cooled nitrobenzene (15 ml.) at such a rate that the temperature did not exceed 5°. The mixture was kept thereat for a further 3 hr., and then at room temperature for 2 days with occasional stirring. The product was hydrolysed, nitrobenzene removed with steam, and the precipitate filtered off and digested with sodium carbonate solution. The clear alkaline filtrate (charcoal) was acidified, and the red precipitate was filtered off, washed with cold water, and dried (*ca.* 2·8 g.). On repeated crystallisation from benzene, the *keto-acid* formed pink needles, m. p. 181·5—182·5° (Found : C, 69·8; H, 4·7; OMe, 20·6. $C_{19}H_{16}O_5$ requires C, 70·2; H, 4·9; OMe, 19·1%). Its *methyl ester* crystallised from benzene in red, lustrous crystals, m. p. 117—118° (Found : C, 71·3; H, 5·1; OMe, 28·5. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3; OMe, 27·4%), its **2 : 4-dinitrophenylhydrazone** crystallised from glacial acetic acid in red needles, m. p. 262—263° (Found : N, 11·0. $C_{26}H_{22}O_7N_4$ requires N, 10·8%).

2-Acetoxy-2′ : 7-dimethoxy-3 : 4-benzofluorenone (VI; R = R_2 = H, R_1 = R_3 = OMe, R″ = Ac).—A mixture of the above keto-acid (3 g.), sodium acetate (1 g.), and acetic anhydride (20 ml.) was refluxed for 3 hr. Decomposition of acetic anhydride precipitated a red product which was extracted with benzene. The extract was washed with water and then with sodium carbonate solution and dried ($CaCl_2$). The solid (*ca.* 3·2 g.) left on the evaporation of the solvent was crystallised from benzene, giving **2-acetoxy-2′ : 7-dimethoxy-3 : 4-benzofluorenone** in red crystals, m. p. 210—211° (Found : C, 72·3; H, 4·6; OMe, 17·9. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6; OMe, 17·8%).

2-Hydroxy-2′ : 7-dimethoxy-3 : 4-benzofluorenone (VI; R = R_2 = R″ = H, R_1 = R_3 = OMe).—Hydrolysis of acetoxybenzofluorenone with aqueous sodium hydroxide and working up as usual gave the hydroxy-compound, dark-red flakes, m. p. above 320° (from benzene). It was best identified as its methyl ether, which was prepared as follows :

(*a*) A mixture of the above benzofluorenone (0·4 g.), acetone (15 ml.), methyl iodide (2·5 ml.), and potassium carbonate (1·4 g.) was refluxed for 14—16 hr. and worked up as usual. The

product was extracted with benzene, and the extract washed with sodium hydroxide solution, followed by water, and dried ($CaCl_2$). Distillation of the solvent and crystallisation of the red solid (*ca.* 0·4 g.) from benzene gave **2** : **2′** : **7**-*trimethoxy*-**3** : **4**-*benzofluorenone*, m. p. **183—184°** (Found : C, 75·2; H, 4·9; OMe 29·0. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0; OMe, 29·2%).

(*b*) *Cyclisation* of **4** : **6**-*dimethoxy*-**1**-p-*methoxyphenyl*-**2**-*naphthoic acid* (II; R = R_2 = R′ = H, R_1 = R_3 = OMe, R″ = Me). A mixture of the pure acid (0·4 g.), benzene (15 ml.), and phosphoric oxide (3 g.) was refluxed for 2 hr. Distillation of benzene and crystallisation of the red solid (0·35 g.) from the same solvent gave the trimethoxy-compound in aggregates, m. p. and mixed m. p. **183—184°**.

Ethyl Hydrogen γγ-Di-o-*methoxyphenylitaconate* (I; R = R_2 = OMe, R_1 = R_3 = H, R′ = Et).—A mixture of **2** ; **2′**-dimethoxybenzophenone (6·1 g.), diethyl succinate (6·5 g.), and a solution of potassium *tert.*-butoxide (from 1·1 g. of metal) in *tert.*-butyl alcohol (25 ml.) was refluxed in nitrogen; the further procedure was essentially the same as that used by Johnson *et al.* (*loc. cit.*) for the **4** : **4′**-dimethoxy-analogue. The crude product (*ca.* 3·7 g.) on crystallisation from benzene afforded *ethyl hydrogen γγ-di*-o-*methoxyphenylitaconate*, m. p. **153—154°** (efferv.) (Found : C, 68·1; H, 5·8; OMe, 23·1; active H, 0·3. $C_{21}H_{22}O_6$ requires C, 68·1; H, 5·9; OMe, 23·1; active H, 0·3%).

Attempts to carry out the above condensation by use of alcoholic potassium ethoxide or its suspension in benzene (cf. Haworth and Sheldrick, *J.*, 1935, 640) and long refluxing (17—40 hr.) always gave a very poor yield of an uncrystallisable half-ester. The neutral fraction was hydrolysed with 10% aqueous sodium hydroxide, and the insoluble product extracted with benzene. Distillation of the solvent left a residue which crystallised from methanol to give di-*o*-methoxyphenylmethanol, m. p. **85—86°**. Ziegler and Ochs (*Ber.*, 1922, **55**, 2273) gave m. p. 85—86° (Found : C, 73·5; H, 6·4; active H, 0·4%; *M*, 227. Calc. for $C_{15}H_{16}O_3$: C, 73·8; H, 6·5; active H, 0·4%; *M*, 244).

γγ-Di-o-*methoxyphenylitaconic Acid* (I; R = R_2 = OMe, R_1 = R_3 = R′ = H).—The half-ester (4 g.), when hydrolysed with 10% aqueous-alcoholic potassium hydroxide, gave the crude *acid* (*ca.* 3·7 g.), which had m. p. **185—186°** after crystallisation from dilute acetic acid (Found : C, 66·1; H, 5·2; OMe, 17·7. $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·2; OMe, 18·1%).

This acid (4 g.) and acetyl chloride (20 ml.) were refluxed for an hour, the excess of chloride was removed (reduced pressure), and the pale yellow crystalline residue was washed with sodium hydrogen carbonate solution, followed by water, and dried The *anhydride* was then obtained (*ca.* 3·7 g.); on crystallisation from benzene–light petroleum (b. p. 40—60°) it had m. p. **140—141°** (Found : C, 70·7; H, 5·1; OMe, 19·3. $C_{19}H_{16}O_5$ requires C, 70·4; H, 4·9; OMe, 19·1%).

4-*Hydroxy*-**8**-*methoxy*-**1**-o-*methoxyphenyl*-**2**-*naphthoic Acid* (II; R = R_2 = OMe, R_1 = R_3 = R′ = R″ = H).—A mixture of the above half-ester (2 g.), sodium acetate (4 g.), and acetic anhydride (10 ml.) was refluxed for 6 hr. and worked up as usual. *Ethyl* **4**-*acetoxy*-**8**-*methoxy*-**1**-*o*-*methoxyphenyl*-**2**-*naphthoate* was obtained as a pale brown, viscous oil, but 2 hours' refluxing with 10% alcoholic potassium hydroxide and working up as usual afforded the crude acid (*ca.* 1·7 g.); trituration with benzene and crystallisation from acetic acid gave crystals, m. p. **246—247°** (Found : C, 69·7; H, 4·8. $C_{19}H_{16}O_5$ requires C, 70·2; H, 4·8%). It did not give a **2** : **4**-dinitrophenylhydrazone. Its *ethyl ester* had m. p. **162—163°** (from benzene) (Found : C, 71·5; H, 5·6; OMe, 24·8. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·7; OMe, 26·4%).

4 : **8**-*Dimethoxy*-**1**-*o*-*methoxyphenyl*-**2**-*naphthoic Acid* (II; R = R_2 = OMe, R_1 = R_3 = R′ = H, R″ = Me).—A hot mixture of the foregoing acid (2 g.), acetone (20 ml.), and potassium carbonate (4 g.) was treated portionwise with methyl iodide (6 g.) during 12 hours' refluxing and then worked up as usual. The pale brown oily product was extracted with benzene, and the extract washed and dried ($CaCl_2$). Distillation of benzene left methyl **4** : **8**-dimethoxy-**1**-*o*-methoxyphenyl-2-naphthoate as a pale brown oil. It was therefore hydrolysed with 10% alcoholic potassium hydroxide to the *acid* (2·0 g.), which recrystallised from glacial acetic acid and then had m. p. **175—176°** (Found : C, 71·5; H, 5·4; OMe, 26·4. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3; OMe, 27·4%).

4 : **8**-*Dimethoxy*-**1**-*o*-*methoxyphenylnaphthalene* (III; R = R_2 = OMe, R_1 = R_3 = H).—The above acid (II; R = R_2 = OMe, R_1 = R_3 = R′ = H; R″ = Me) (0·4 g.) was decarboxylated with copper-bronze (0·4 g.) in quinoline (4 ml.), exactly as described for the *p*-isomer. Distillation of the solvent and crystallisation of the residue from light petroleum (b. p. 80—100°) gave **4** : **8**-*dimethoxy*-**1**-*o*-*methoxyphenylnaphthalene*, m. p. **111—112°** (Found : C, 78·1; H, 6·1; OMe, 30·6. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1; OMe, 31·8%).

Attempted Preparation of **2** : **4′** : **5**-*Trimethoxy*-**3** : **4**-*benzofluorenone* (VI; R = R_2 = OMe, R_1 = R_3 = H, R″ = Me).—A mixture of **4** : 8-dimethoxy-1-*o*-methoxyphenyl-2-naphthoic

acid (1·5 g.), phosphoric oxide (2·5 g.), and benzene (20 ml.) was worked up as described for the *p*-isomer. Distillation of the solvent left a dark, cherry-red viscous oil (*ca.* 1·2 g.), a fraction, b. p. 260—290°/2 mm., of which solidified to a dark red, uncrystallisable mass.

Action of Aluminium Chloride on γγ-Di-o-methoxyphenylitaconic Anhydride (IV; R = R_2 = OMe, R_1 = R_3 = H).—Finely powdered aluminium chloride (1·5 g.) was gradually added to a stirred solution of the anhydride (3 g.) in nitrobenzene (30 ml.) at 0—5°, and the mixture left for 2 days (20—25°), and then worked up as usual. The pale brown product was filtered off, and digested with sodium carbonate solution. Acidification of the clear filtrate (charcoal) precipitated an acid which was filtered off, washed, and dried (*ca.* 2·7 g.). On crystallisation from benzene–light petroleum (b. p. 40—60°), *4-o-methoxyphenyl-3-coumarinylacetic acid* was obtained, m. p. 185—186° (depressed to 158—176° on admixture with γγ-di-*o*-methoxyphenylitaconic acid) (Found: C, 69·9; H, 4·8; OMe, 10·6. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·7; OMe, 10·0%). It discharged the colour of alkaline potassium permanganate solution and failed to give a 2 : 4-dinitrophenylhydrazone.

Conversion of 4-o-Methoxyphenyl-3-coumarinylacetic Acid (VII) *into αα-Di-o-methoxyphenylitaconic Acid* (I; R = R_2 = OMe, R_1 = R_3 = R′ = H).—A solution of the acid (VII) (0·3 g.) in sodium hydroxide (0·3 g.) and water (1 ml.) was refluxed for 30 min. and kept on a water-bath while being treated portionwise with methyl sulphate (0·32 g.) (cf. Stoermer and Friemel, *Ber.*, 1911, **44**, 1843) for an hour thereafter. The product was extracted with ether, and the extract washed successively with sodium hydroxide solution and with water and dried (Na_2SO_4). Distillation of ether left a viscous, pale brown oil which was directly hydrolysed with 10% alcoholic potash (3 hours' refluxing). The clear aqueous solution (charcoal) was acidified, and the precipitate was filtered off (*ca.* 0·3 g.), and crystallised from dilute acetic acid, giving γγ-di-*o*-methoxyphenylitaconic acid, identical with an authentic specimen.

3-Iodoanisic Acid.—Finely powdered anisic acid (14·8 g.) was iodinated by the method used by Derbyshire and Waters (*loc. cit.*) for iodobenzoic acid, and the precipitate thoroughly extracted with sodium carbonate solution. The clear alkaline extract (charcoal) was acidified, and the precipitate washed and dried (*ca.* 25 g.). On crystallisation from ethyl alcohol, 3-iodoanisic acid was obtained in needles, m. p. 234—235° (Willgerodt and Burkhard, *Annalen*, 1912, **389**, 294, gave m. p. 234°). Its methyl ester crystallised from light petroleum (b. p. 60—80°) in flakes, m. p. 94—95° (Found: C, 37·2; H, 3·1; OMe, 20·8; I, 43·2. Calc. for $C_9H_9O_3I$: C, 36·9; H, 3·1; OMe, 21·4; I, 43·5%).

Attempted Synthesis of 4 : 8-Dimethoxy-1-o-methoxyphenylnaphthalene by Gomberg's Reaction.—Methyl 3-aminoanisate (9 g.) (von Auwers, *Ber.*, 1897, **30**, 1477) was diazotised, and the solution mixed with one of 1 : 5-dimethoxynaphthalene (Naylor and Gardner, *J. Amer. Chem. Soc.*, 1931, **53**, 4109) (19·2 g.) in carbon tetrachloride (100 ml.); the mixture was stirred at −5° while sodium hydroxide solution (25 ml.; 60%) was gradually added (1 hr.). The temperature was kept at −10° for 1·5 hr., raised to 45° during 3·5 hr., and kept thereat for 5 hr., and the mixture worked up as described by Baddar (*J.*, 1941, 310). Products isolated from both the carbon tetrachloride layer and the sodium hydroxide layer were either uncrystallisable oils or mixtures of crystals, and the yields were so poor that no pure constituents could be separated.

Faculty of Science, The Cairo University,
Orman, Cairo.

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Experiments in the Synthesis of DL-isoLeucine.

By F. P. Doyle, D. O. Holland, W. Marflitt, J. H. C. Nayler, and (Miss) C. M. O'Connor.

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The crude products of numerous syntheses of DL-*iso*leucine have been found to contain substantial amounts of the *allo*-modification. Possible stereospecific routes to the amino-acid starting from 4-*sec.*-butylidene-2-phenyloxazol-5-one and 4-*sec.*-butylidene-2-thiothiazolid-5-one have been investigated and also found to give mixtures of the two forms.

In most of the recorded syntheses of *iso*leucine the simultaneous formation of *alloiso*leucine has been either cursorily dismissed or ignored altogether. We have therefore applied most of the classical and some newer methods of amino-acid synthesis to the preparation of this amino-acid and have assayed the crude products, microbiologically, for their *iso*leucine content. As shown in the following Table however, none led to *iso*leucine of high purity. In some routes minor modifications were made to the original published details and in most cases the isolation of the crude amino-acid mixture was effected by treating alcoholic solutions of the hydrochlorides with triethylamine.

Route	DL-*iso*Leucine (%) in crude material	Route	DL-*iso*Leucine (%) in crude material
Organic Syntheses [a]	89 *	Darapsky [e]	42
Oximino-acid [b]	66	Strecker [f]	68
Feofilaktov [c]	64	Bucherer–Bergs [g]	61
Schmidt † [d]	72		

a, Marvel, *Org. Synth.*, 1941, **21**, 60. *b*, Hamlin and Hartung, *J. Biol. Chem.*, 1942, **145**, 349. *c*, Feofilaktov, *Compt. rend. Acad. Sci., U.R.S.S.*, 1939, **42**, 755. *d*, Schmidt, *Ber.*, 1924, **57**, 704 (cf. *Organic Reactions*, 1946, **3**, 316). *e*, Gagnon *et al.*, *Canad. J. Res.*, 1947, **25**, *B*, 28. *f*, Gresham and Schweitzer, U.S.P. 2,520,312. *g*, Livak *et al.*, U.S.P. 2,553,055.

* The high proportion of *iso*leucine in the crude material arises here because the method of working up includes a crystallisation which increases the percentage of *iso*leucine in the product at the expense of overall yield.

† This reaction has not previously been applied to the preparation of *iso*leucine and details are given on p. 1720.

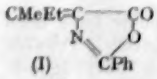
A convenient method for the separation of *iso*leucine from *alloiso*leucine by ion-exchange chromatography has recently been published (Piez, *J. Biol. Chem.*, 1954, **207**, 77), but before this only tedious methods were available (cf. Hood and Lyman, *J. Biol Chem.*, 1950, **186**, 195; Shabica, U.S.P. 2,456,742). We therefore examined two further syntheses involving αβ-unsaturated intermediates in the hope that the *cis-trans*-isomers could be separated, and then reduced and hydrolysed stereospecifically.

Lur'e and Vdovina (*Zhur. obshchei Khim.*, 1952, **22**, 1883) catalytically hydrogenated 4-*sec.*-butylidene-2-phenyloxazol-5-one (I), prepared from hippuric acid and ethyl methyl ketone, and hydrolysed the product to α-amino-β-methylvaleric acid. We obtained a mixture of both forms of the amino-acid by the action of red phosphorus and hydriodic acid on the oxazolone. Lur'e and Vdovina (*loc. cit.*) separated the isomers of the oxazolone (I) in an indirect manner and converted them into the two α-benzamido-β-ethyl-β-methylacrylic acids (II) and various derivatives thereof. We obtained the acid (II) as a mixture of isomers by hydrolysis of the crude oxazolone and separated one apparently pure isomer, m. p. 221—222°, by crystallisation.

This acid was readily hydrogenated over Raney nickel to α-benzamido-β-methylvaleric acid which on subsequent acid hydrolysis gave a specimen of amino-acid containing 78% of *iso*leucine. From the crystallisation mother-liquors of the acid (II), m. p. 221—222°, another acid, of m. p. 203°, was obtained which on hydrogenation gave a mixture of N-benzoyl*iso*leucine and *N*-benzoyl*alloiso*leucine.

Experiments in which pure specimens of *N*-benzoyl*iso*leucine and *N*-benzoyl*alloiso*leucine were hydrolysed under conditions identical with those employed for the reduction

products indicated that slight inversion occurred during hydrolysis, but insufficient to account for the low figure of 78% of *iso*leucine obtained from the pure acid of m. p. 221—222°, and this has led us to suspect that the reduction with Raney nickel may not be completely stereospecific. Taken in conjunction with the inversion during hydrolysis this would therefore limit the value of α-benzamido-β-ethyl-β-methylacrylic acid (m. p. 221—222°) as an intermediate for the preparation of pure *iso*leucine.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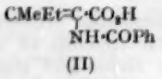
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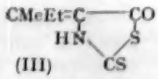
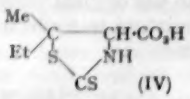

(III)

Possible syntheses via 4-*sec.*-butylidene-2-thiothiazolid-5-one (III), which is readily obtained by the condensation of 2-thiothiazolid-5-one with ethyl methyl ketone (cf. Billimoria and Cook, *J.*, 1949, **2323**; Cook, Hunter, and Pollock, *J.*, 1950, **1892**), were next examined. This compound, however, could not be separated into *cis-trans*-isomers, although reductive hydrolysis with red phosphorus and hydriodic acid according to the general procedure of Billimoria and Cook (*loc. cit.*) gave a mixture of approximately equal amounts of both forms of the amino-acid.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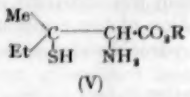
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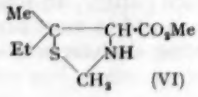
(VI)

Treatment of (III) with an excess of methanolic potassium hydroxide according to the general procedure of Chatterjee, Cook, Heilbron, and Levy (*J.*, 1948, **1337**) readily yielded 5-ethyl-5-methyl-2-thiothiazolidine-4-carboxylic acid (IV), as a low-melting, deliquescent solid conveniently isolated as the highly crystalline phenethylamine salt. 4-Benzylidene-2-thiothiazolid-5-one yields one isomer of 5-phenyl-2-thiothiazolidine-4-carboxylic acid on treatment with methanolic potassium hydroxide, and the other isomer with aqueous sodium carbonate (Chatterjee *et al.*, *loc. cit.*), but the *sec.*-butylidene analogue (III) failed to react with cold aqueous sodium carbonate and after 2 hours' boiling gave only 23% of the acid obtained previously.

Vigorous treatment of the acid (IV) with hydrochloric acid (cf. Cook *et al.*, *J.*, 1948, **1060**; 1949, **1437**, **3007**) afforded the hydrochloride of α-amino-β-mercapto-β-methylvaleric acid (V; R = H), previously obtained from 4-*sec.*-butylidene-2-methyloxazolone and hydrogen sulphide ("The Chemistry of Penicillin," Oxford, 1949, p. 469). The hydrochloride of the corresponding ester (V; R = Me) was obtained from the acid (IV) by successive *S*-methylation, esterification, reduction with aluminium amalgam, and treatment of the resulting methyl 5-ethyl-5-methylthiazolidine-4-carboxylate (VI) with mercuric chloride (cf. Cook, Hunter, and Pollock, *loc. cit.*). Unfortunately attempts to desulphurise the mercapto-amino-acid (V; R = H) by treatment with Raney nickel or with phosphorus and hydriodic acid failed to yield any *iso*leucine or *alloiso*leucine.

Experimental

The L-*iso*leucine assays were carried out by Hood and Lyman's method (*loc. cit.*) and the results doubled to give the percentages of DL-*iso*leucine shown in the Table: the organisms employed were *S. faecalis* and *Leuc. mesenteroides*.

Schmidt Reaction on Ethyl α-sec.-Butylacetoacetate.—Ethyl α-*sec.*-butylacetoacetate (9·3 g.) in dry chloroform (60 ml.) was treated with hydrazoic acid in chloroform (42·6 ml. of 7·58% w/v solution), and the mixture was added dropwise during 1 hr. to a vigorously stirred mixture of concentrated sulphuric acid (40 ml.) and chloroform (40 ml.) kept at −5° to 0°. The mixture was stirred for 30 min. at the same temperature and then poured on ice. The aqueous phase was extracted with chloroform, and the combined chloroform solutions were washed, dried (Na_2SO_4), and evaporated *in vacuo* to leave crude ethyl α-acetamido-β-methylvalerate (*ca.* 10 g.). This oil was refluxed overnight with 5N-hydrochloric acid (80 ml.) and, after treatment

with charcoal, the solution was evaporated *in vacuo*. The solid residue was dissolved in ethanol and treated with triethylamine to pH 6 to precipitate the amino-acid, which was collected and thoroughly washed with ethanol. The yield was 3·02 g. (46%).

4-sec.-*Butylidene-2-phenyloxazol-5-one.*—Acetic anhydride (76 ml.) was added dropwise during 30 min. to a stirred suspension of hippuric acid (54 g.) and anhydrous sodium acetate (24 g.) in ethyl methyl ketone (1300 ml.), and the mixture was refluxed for 2 hr. About 1050 ml. of ketone, b. p. 80—84°, were next distilled off during 2—3 hr. The oily residue was diluted with water (300 ml.), and sodium hydrogen carbonate (*ca.* 190 g.) was added until effervescence ceased. The product was extracted into ether and distilled, to give the mixed isomers as a pale yellow oil, b. p. 107—120°/0·15 mm. (43—49%), which partly solidified.

Reduction of the Oxazolone (I).—A mixture of the oxazolone (21·2 g.), acetic acid (140 ml.), hydriodic acid (100 ml.; 55% w/w), and red phosphorus (6 g.) was refluxed for 90 min. and filtered from unchanged phosphorus. The filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in water and freed from benzoic acid by ether-extraction. After evaporation of the aqueous phase *in vacuo* the residue was dissolved in ethanol, and the solution adjusted to pH 6 with triethylamine (15 ml.). The white precipitate was collected and heated on the steam-bath for 1 hr. with an aqueous suspension of calcium hydroxide and, after removal of calcium phosphate, the filtrate was freed from calcium by addition of ammonium carbonate and filtration. Evaporation of the final filtrate *in vacuo* left 5·38 g. (42%) of amino-acid (washed with alcohol). Microbiological assay indicated the presence of 50% of *iso*leucine, raised to 58% by a single crystallisation from aqueous alcohol.

Hydrolysis of the Oxazolone (I).—The oxazolone (28 g.) was heated on the steam-bath for 45 min. with methanol (72 ml.) and 2N-sodium hydroxide (87 ml.), and the cooled solution was made strongly acid to precipitate α-benzamido-β-ethyl-β-methylacrylic acid, m. p. 193—195° (decomp.) (27 g., 89%). Three crystallisations from ethanol gave 7·9 g. of a component, m. p. 221—222° not increased by further crystallisation from ethanol or acetic acid (Found: C, 66·7; H, 6·6; N, 6·2. Calc. for $C_{13}H_{15}O_3N$: C, 66·9; H, 6·4; N, 6·0%), which with ethereal diazomethane yielded a methyl ester, m. p. 158° (Found: C, 68·0; H, 6·9; N, 5·8. Calc. for $C_{14}H_{17}O_3N$: C, 68·0; H, 6·9; N, 5·7%). Lur'e and Vdovina (*loc. cit.*) give the m. p. of these compounds as 223—224° and 155—156° respectively. From the ethanol mother-liquors were obtained 6·3 g. of a mixture of isomers, constant m. p. 203° (Found: C, 67·2; H, 6·8; N, 6·4%).

N-*Benzoyl*-iso*leucine and* -alloiso*leucine.*—Pure *iso*leucine (Hood and Lyman, *loc. cit.*) (13·1 g.) in 10% aqueous sodium hydroxide (80 ml.) was treated gradually at 0° with benzoyl chloride (20 ml.) and 20% aqueous sodium hydroxide (40 ml.) during 30 min., so that the mixture remained alkaline throughout. Acidification afforded N-*benzoyl*-DL-iso*leucine* (20·7 g., 88%) which after one crystallisation from 30% aqueous alcohol formed colourless plates, m. p. 136—138° unchanged on further crystallisation from this solvent or from benzene (Found: C, 66·5; H, 7·5; N, 6·1. $C_{12}H_{17}O_3N$ requires C, 66·3; H, 7·3; N, 6·0%). In the same way *alloiso*leucine (Greenstein, Levintow, Baker, and White, *J. Biol. Chem.*, 1951, **188**, 647) gave N-*benzoyl*-DL-alloiso*leucine*, colourless needles (from benzene), m. p. 126—127° (Found: C, 66·0; H, 7·0; N, 6·0%). A mixture of approximately equal amounts of the isomers had m. p. 112—114°. The only optically inactive α-benzamido-β-methylvaleric acid reported hitherto is the product, m. p. 118°, which Bouveault and Locquin (*Bull. Soc. chim. France*, 1906, **35**, 965) considered to be benzoyl*iso*leucine, but which probably contained the *allo*-modification.

iso*Leucine and* alloiso*Leucine.*—α-Benzamido-β-ethyl-β-methylacrylic acid, m. p. 221—222° (6·13 g.), in 1% aqueous sodium hydroxide (105 ml.) was hydrogenated at room temperature and pressure over Raney nickel (13 hr.). Acidification of the filtered reaction product gave α-benzamido-β-methylvaleric acid, m. p. 132—133° (6·06 g., 90%). Mixtures with *N*-benzoyl-*iso*leucine and *-alloiso*leucine melted at 135—137° and 112—114° respectively. The crude product (4·82 g.) and 20% hydrochloric acid (80 ml.) were refluxed together for 3 hr. and the resulting solution was evaporated to dryness *in vacuo* after removal of benzoic acid. The residue was dissolved in ethanol and treated with triethylamine to pH 6, and the precipitate (2·41 g., 89%) was collected and washed with ethanol until free from chloride. It was estimated to contain 78% of *iso*leucine, raised to 88% by one crystallisation.

Similar treatment of crude α-benzamido-β-ethyl-β-methylacrylic acid, m. p. 193—195° (decomp.), gave 86% of a mixture of *N*-benzoyl-*iso*leucine and *-alloiso*leucine, m. p. 112—114°, which on hydrolysis afforded 82% of amino-acid estimated to contain 62% of *iso*leucine. The acid, m. p. 203°, from the mother-liquors of the crystallisation of (II) gave 89% of a reduction product, m. p. 116—118°.

The specimens of amino-acid obtained when authentic *N*-benzoyl-*iso*leucine and *-alloiso*-leucine were hydrolysed as described were estimated to contain 90% and 17% respectively of *iso*leucine.

4-sec.-*Butylidene-2-thiothiazolid-5-one.*—(*a*) A suspension of 2-thiothiazolid-5-one (50 g.) in ethyl methyl ketone (800 ml.) was treated with benzylamine (1·5 ml.) and after agitation for a few minutes the clear purple solution was set aside with daily additions of 0·5-ml. quantities of benzylamine until, after 3—14 days, the presence of 2-thiothiazolid-5-one could no longer be detected (cf. Billimoria and Cook, *loc. cit.*). The mixture was diluted with water (1 l.), and the crude product (59—94%) was collected and crystallised from alcohol (charcoal), to give straw-yellow platelets, m. p. 180—181°. 4-sec.-*Butylidene-2-thiothiazolid-5-one* also crystallised well from ethyl methyl ketone (Found: C, 44·8; H, 5·2; N, 7·1. $C_7H_9ONS_2$ requires C, 44·9; H, 4·8; N, 7·5%).

(*b*) A suspension of 2-thiothiazolid-5-one (23 g.) and anhydrous zinc chloride (23 g.) in ethyl methyl ketone (207 ml.) was refluxed with stirring for 6 hr., and the product cooled and diluted with water (600 ml.). The crude green precipitate (22·6 g., 70%) was purified as in (*a*).

Reduction of the Thiazolidone (III).—A solution of 4-*sec.*-butylidene-2-thiothiazolid-5-one (6 g.) in boiling acetic acid (50 ml.) was treated with red phosphorus (3 g.) and hydriodic acid (20 ml.; 40% w/w). The mixture was refluxed for 6 hr. and worked up as described for the reduction of the oxazolone (I), to yield 2·60 g. (62%) of amino-acid, which was estimated to contain 48% of *iso*leucine.

Phenethylamine 5-Ethyl-5-methyl-2-thiothiazolidine-4-carboxylate.—4-*sec.*-Butylidene-2-thiothiazolid-5-one (28 g.) was heated on the steam-bath for 20 min. with potassium hydroxide (33·6 g.) in methanol (400 ml.), and the resulting yellow solution was set aside for 3 days, then evaporated *in vacuo*. The residue was treated with 5N-hydrochloric acid, and the gummy product was extracted into chloroform. The washed and dried chloroform solution was concentrated to small volume, cooled, and treated with phenethylamine (18 g.), to give a colourless precipitate of the almost pure *phenethylamine salt* (37·5 g., 77%) which crystallised from water in needles, m. p. 182—183° (decomp.) (Found: C, 55·4; H, 6·6; N, 8·4; S, 19·8. $C_{15}H_{22}O_2N_2S_2$ requires C, 55·2; H, 6·8; N, 8·6; S, 19·6%).

α-Amino-β-mercapto-β-methylvaleric Acid Hydrochloride.—The low-melting acid (IV), regenerated from the phenethylamine salt (3·63 g.), was heated with concentrated hydrochloric acid (40 ml.) in a sealed tube at 120° for 40 hr. After evaporation to dryness *in vacuo* the sticky residue was further dried in a vacuum-desiccator over potassium hydroxide, washed with ether, and crystallised from acetonitrile, to give small colourless crystals of the hydrated *hydrochloride* (54%), m. p. 112—115°. Recrystallisation raised the m. p. to 114—116° (Found: C, 33·3; H, 7·5; S, 14·7. Calc. for $C_6H_{14}O_2NSCl,H_2O$: C, 33·1; H, 7·4; S, 14·7%). The anhydrous material, considered to be a mixture of isomers, has been reported to be very hygroscopic and of indefinite m. p. (*op. cit.*, p. 469). The neutral amino-acid gave an intense purple colour with ferric chloride and a crimson colour with ninhydrin.

5-Ethyl-5-methyl-2-methylthio-Δ^2-thiazoline-4-carboxylic Acid.—The acid (IV), from 32·6 g. of the phenethylamine salt, was dissolved in dry acetone (100 ml.) and treated with anhydrous potassium carbonate (30 g.) and methyl iodide (7 ml.). The stirred mixture was refluxed for 2 hr. and, after removal of the solvent *in vacuo*, the residue was dissolved in water, and the solution was brought to pH 4 by cautious addition of dilute hydrochloric acid. The amphoteric product was extracted into ether (6 × 75 ml.), and the gum remaining after evaporation of the dried extracts was triturated with light petroleum (b. p. 40—60°) to give a cream-coloured powder (16·1 g.). Crystallisation from light petroleum (b. p. 60—80°) gave colourless needles of *5-ethyl-5-methyl-2-methylthio-Δ^2-thiazoline-4-carboxylic acid*, m. p. 101—103° (Found: C, 43·3; H, 6·0; N, 6·7; S, 29·3. $C_8H_{13}O_2NS_2$ requires C, 43·8; H, 6·0; N, 6·4; S, 29·2%).

Methyl 5-Ethyl-5-methylthiazolidine-4-carboxylate.—The *S*-methylated acid (11 g.) was esterified with ethereal diazomethane, and the resulting oil was dissolved in methanol and added to aluminium amalgam (from 10 g. of aluminium foil and 200 ml. of 3% mercuric chloride solution). Methanethiol was evolved and the mixture boiled spontaneously. When the reaction had subsided the mixture was refluxed for 90 min. and filtered, and the solid was washed with hot methanol. The colourless filtrate and washings were evaporated *in vacuo* and the residual oily *ester* (6·05 g., 64%) was distilled at 75—95°/0·3—0·4 mm. A redistilled specimen had b. p. 74°/0·2 mm., n_D^{25} 1·4992 (Found: C, 50·9; H, 7·7. $C_8H_{15}O_2NS$ requires C, 50·8; H, 8·0%).

Methyl α-Amino-β-mercapto-β-methylvalerate Hydrochloride.—The ester (VI) (4·1 g.) was refluxed with mercuric chloride (20 g.) in methanol (200 ml.) for 2 hr. and the mixture was set

aside overnight, saturated with hydrogen sulphide, and filtered. Evaporation of the colourless filtrate *in vacuo* left the crude ***hydrochloride*** (3·28 g., 71%), which crystallised from ethyl acetate in colourless needles, m. p. *ca.* 153—155° (decomp.) dependent on the rate of heating (Found: C, 39·8; H, 7·8; S, 14·6; Cl, 16·7. $C_7H_{16}O_3NSCl$ requires C, 39·3; H, 7·6; S, 15·0; Cl, 16·6%). An aqueous solution neutralised with sodium hydrogen carbonate gave an intense purple colour with ferric chloride.

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MEDICINAL CHEMISTRY DIVISION, BEECHAM RESEARCH LABORATORIES LTD.,
BETCHWORTH, SURREY.
C. L. BENCARD, LTD., MINERVA ROAD,
PARK ROYAL, LONDON, N.W.10.

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The Conversion of cyclo*Hexanone into* 1 : 1-*Disubstituted* cyclo*Hexanes.*

By W. PARKER and R. A. RAPHAEL.

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*cyclo*Hexanone has been converted into 1 : 1-dimethyl-, 1-methyl-1-vinyl-, 1-formyl-1-methyl-, and 1-carboxy-1-methyl-*cyclo*hexane. The bearing of these results on synthetical problems in the diterpenoid field is discussed.

ONE of the characteristic properties of diterpenoid and triterpenoid structures is the frequent occurrence of disubstituted carbon atoms in one or more of the six-membered rings. This feature constitutes a considerable obstacle to the synthesis of these compounds, especially when the two groupings are dissimilar. This difficulty was recently clearly shown by the synthesis of a tricyclic ketone possessing the carbon skeleton of dehydroabietic acid, with the exception of the *gem*-methyl–carboxylic acid feature, these two radicals being replaced by an oxo-group (Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 3544). This communication describes a method for the introduction of *gem*-disubstitution in place of such an oxo-group and the use of the method to procure any of the *gem*-groupings typical of terpenoid structures.

*cyclo*Hexanone was used as the model ketone. This was converted into ethyl α-cyano-*cyclo*hexylideneacetate by the well-known ammonium acetate technique. Interaction of this ester and methylmagnesium iodide resulted in conjugate addition to the double bond with the production of ethyl α-cyano-1-methyl*cyclo*hexylacetate (Robinson and Birch, *J.*, 1943, 501; Alexander, McCollum, and Paul, *J. Amer. Chem. Soc.*, 1950, **72**, 4791). The nitrile group in this compound was very resistant to complete hydrolysis; aqueous or alcoholic alkali gave only 1-methyl*cyclo*hexylmalonamic acid while acid hydrolysis proceeded even less completely, the corresponding cyano-acid being the sole product. Ultimately complete hydrolysis to 1-methyl*cyclo*hexylmalonic acid was achieved by employing potassium hydroxide in ethylene glycol, and decarboxylation of this acid furnished 1-methyl*cyclo*hexylacetic acid. Treatment of silver 1-methyl*cyclo*hexylacetate with bromine in ethyl bromide gave 1-bromomethyl-1-methyl*cyclo*hexane, reductive debromination of which with zinc and acetic acid furnished 1 : 1-dimethyl*cyclo*hexane.

Methyl 1-methyl*cyclo*hexylacetate was reduced by lithium aluminium hydride to 1-2′-hydroxyethyl-1-methyl*cyclo*hexane. Dehydration of this alcohol by means of boric acid (Brandenberg and Galat, *J. Amer. Chem. Soc.*, 1950, **72**, 3275) gave 1-methyl-1-vinyl*cyclo*hexane.

Hofmann degradation of 1-methyl*cyclo*hexylmalonamic acid led to the corresponding

α-amino-acid, 1-methyl*cyclo*hexylglycine, Strecker degradation of which with sodium hypochlorite gave 1-formyl-1-methyl*cyclo*hexane. As an alternative route to this aldehyde, 1-methyl*cyclo*hexylmalonic acid was converted into its dihydrazide which was then subjected to a double Curtius degradation. Acid hydrolysis of the resulting diurethane produced the aldehyde, identical with that prepared by the first route. In an attempted third route to the aldehyde, 1-methyl*cyclo*hexylmalononitrile was prepared by the addition of methylmagnesium iodide to *cyclo*hexylidenemalononitrile; mild hydrolysis furnished the corresponding diamide. Attempted double Hofmann degradation of the diamide was unsuccessful; only one of the amide groups was affected and the major product was the hydantoin of 1-methyl*cyclo*hexylglycine, proof of structure being obtained by hydrolysis to the amino-acid (cf. Rinkes, *Rec. Trav. chim.*, 1927, **46**, 271).

1-Methyl*cyclo*hexanecarboxylic acid was obtained by a Barbier–Wieland degradation of methyl 1-methyl*cyclo*hexylacetate. Another method of obtaining the acid was as follows. Addition of potassium cyanide to the double bond of ethyl α-cyano*cyclo*hexylideneacetate, followed by hydrolysis and esterification produced methyl 1-methoxycarbonyl-*cyclo*hexylacetate (Lapworth and McRae, *J.*, 1922, **121**, 2754). Selective alkaline hydrolysis of the primary ester grouping of this diester furnished 1-methoxycarbonyl*cyclo*hexylacetic acid. Hunsdiecker degradation of this acid (by the action of bromine on the silver salt) gave methyl 1-bromomethyl*cyclo*hexanecarboxylate which was then debrominated by zinc and acetic acid to methyl 1-methyl*cyclo*hexanecarboxylate. Hydrolysis then afforded 1-methyl*cyclo*hexanecarboxylic acid (cf. Saha, Bagchi, and Dutta, *Chem. and Ind.*, 1954, 1143).

Applied to *cyclo*hexanone, both procedures yield the same acid. However, in the first process, the methyl group in the product is derived from the addendum to the double bond of the starting material whereas in the second procedure the addendum provides the carboxyl group. Hence, from an unsymmetrical starting ketone the two methods should afford different epimers as major product; the two procedures are therefore sterically complementary. That methylmagnesium iodide and hydrogen cyanide add in a sterically similar manner is indicated by the results of considerable studies in the steroid field (Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 1949, pp. 328, 376—379, 388, 410; Heusser, Herzig, Fürst, and Plattner, *Helv. Chim. Acta*, 1950, **33**, 1093) although the two processes are not stereospecific to the same degree.

From study of models it can be predicted that application of the second process to the tricyclic ketone obtained by Stork and Burgstahler (*loc. cit.*) should produce racemic dehydroabietic acid, and this supposition is now being tested. The first process should give rise to the epimeric structure in which the methyl and the carboxyl group have the steric relation occurring in podocarpic acid.

Experimental

*Ethyl α-Cyano*cyclo*hexylideneacetate*.—This was prepared by interaction of *cyclo*hexanone and ethyl cyanoacetate in the presence of ammonium acetate, with azeotropic removal of the water formed (Cope *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3452).

*Ethyl α-Cyano-1-methyl*cyclo*hexylacetate*.—To a solution of methylmagnesium iodide [from magnesium (29·2 g.) and methyl iodide (169 g.)] in dry ether (300 c.c.) was added one of ethyl α-cyano*cyclo*hexylideneacetate (193 g.) in ether (300 c.c.) at such a rate that the solvent refluxed gently; thereafter the mixture was heated by steam for 1 hr. It was then poured on crushed ice–ammonium chloride solution (15%), the organic layer separated, and the aqueous layer extracted with fresh ether. Removal of the solvent gave an oil which was treated with concentrated aqueous sodium cyanide (50 g.), followed by sufficient ethanol for dissolution. The solution was set aside overnight, water (1 l.) was then added, and the precipitated oil extracted with benzene. Washing with water, removal of solvent, and distillation gave ethyl α-cyano-1-methyl*cyclo*hexylacetate (139 g.; 67%), b. p. 92°/0·4 mm., n_D^{18} 1·4670.

1-*Methyl*cyclo*hexylmalonic Acid and* 1-*Methyl*cyclo*hexylacetic Acid*.—The above cyano-ester (50 g.) was refluxed with a solution of potassium hydroxide (80 g.) in a mixture of water (80 c.c.) and ethylene glycol (300 c.c.), until ammonia was no longer evolved (10—15 hr.). The mixture

was poured into water (2 l.), and the cold solution acidified with ice-cold sulphuric acid (4N) and thoroughly extracted with ether. Washing with water, drying ($MgSO_4$), and evaporation gave an oily solid which was triturated with light petroleum (b. p. 40—60°). Filtration and crystallisation (ethyl acetate) gave 1-*methyl*cyclo*hexylmalonic acid* (23·7 g.; 50%), as stout needles, m. p. 194—195° (decomp.) (Found: C, 60·0; H, 8·05. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%). With ethereal diazomethane the acid gave the *dimethyl ester*, b. p. 78°/0·35 mm., n_D^{21} 1·4638 (Found: C, 63·35; H, 8·55. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%).

Evaporation of the light petroleum filtrate and distillation produced 1-*methyl*cyclo*hexylacetic acid* (11·3 g.), b. p. 145°/20 mm., n_D^{18} 1·4720 (Found: C, 69·0; H, 10·45. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). More of the acid (26·9 g.; total yield 72%) was obtained by decarboxylation of the above malonic acid at 200°, followed by distillation. The *methyl ester* (prepared with diazomethane) had b. p. 40°/0·4 mm., n_D^{20} 1·4524 (Found: C, 70·6; H, 10·6. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·65%).

1-*Bromomethyl*-1-*methyl*cyclo*hexane*.—The Hunsdiecker degradation was carried out by using Rottenberg's procedure (*Acta Chem. Scand.*, 1953, **7**, 1001). 1-Methyl*cyclo*hexylacetic acid (7 g.) was dissolved in the equivalent quantity of aqueous 0·2N-potassium hydroxide, and a solution of silver nitrate (7·5 g.) in water (100 c.c.) was added; the precipitated silver salt was filtered off, washed successively with water, methanol, acetone, and ether and finally dried at 90°/18 mm. for 12 hr. (10·8 g.; 92%).

An intimate mixture of the silver salt (5 g.) and dry silver acetate (3·04 g.) was covered with dry ethyl bromide (250 c.c.), and the suspension gently heated under reflux. Dry bromine (5·95 g.) was then slowly introduced under the surface in a slow stream of nitrogen and the heating continued for a further hour. After filtration the filtrate was washed successively with potassium iodide solution, sodium thiosulphate solution, and water. Drying ($MgSO_4$), evaporation, and distillation furnished 1-*bromomethyl*-1-*methyl*cyclo*hexane* (3·44 g.; 94%), b. p. 79°/26 mm., $n_D^{17\cdot5}$ 1·4960 (Found: C, 50·05; H, 7·7; Br, 41·45. $C_8H_{15}Br$ requires C, 50·25; H, 7·9; Br, 41·8%).

1 : 1-*Dimethyl*cyclo*hexane*.—Zinc dust (2 g.) was added to a solution of 1-bromomethyl-1-methyl*cyclo*hexane (2 g.) in acetic acid (40 c.c.), and the mixture heated under reflux for 7 hr. The cooled solution was diluted with water (100 c.c.) and extracted with light petroleum (b. p. 40—60°). The extract was washed with sodium carbonate solution and water, and dried (Na_2SO_4). Removal of the solvent followed by fractional distillation at atmospheric pressure gave 1 : 1-dimethyl*cyclo*hexane (0·48 g.; 58%), b. p. 119—121°, $n_D^{21\cdot5}$ 1·4240, and starting material (0·6 g.). (Chavanne, Miller, and Cornet, *Bull. Soc. chim. Belg.*, 1931, **40**, 1673, give b. p. 119·5—120°, n_D^{15} 1·4314.)

1-2′-*Hydroxyethyl*-1-*methyl*cyclo*hexane*.—A solution of 1-methyl*cyclo*hexylacetic acid (11·7 g.) in dry ether (50 c.c.) was added slowly to a slurry of lithium aluminium hydride (5 g.) in ether (400 c.c.). The mixture was heated under reflux for 1 hr. and the excess of reagent then decomposed by ethyl acetate. Working up in the usual manner gave 1-2′-hydroxyethyl-1-methyl*cyclo*hexane (8·85 g.; 83%), b. p. 59°/0·3 mm., $n_D^{20\cdot5}$ 1·4692 (Found: C, 75·85; H, 12·5. Calc. for $C_9H_{18}O$: C, 75·95; H, 12·75%). The 3 : 5-dinitrobenzoate crystallised from ethanol in needles, m. p. 95°. (Schmerling, *J. Amer. Chem. Soc.*, 1949, **71**, 698, records b. p. 82°/3 mm., n_D^{20} 1·4686; 3 : 5-dinitrobenzoate, m. p. 95°.)

1-*Methyl*-1-*vinyl*cyclo*hexane*.—1-2′-Hydroxyethyl-1-methyl*cyclo*hexane (5·55 g.) and boric acid (4·2 g.) were heated to 360°. Ether was added to the moist condensate and the resulting solution dried ($MgSO_4$). Evaporation and distillation gave 1-*methyl*-1-*vinyl*cyclo*hexane* (3·0 g.; 62%), b. p. 80°/95 mm., n_D^{21} 1·4570 (Found: C, 86·95; H, 12·6. C_9H_{16} requires C, 87·0; H, 13·0%). The infrared absorption spectrum showed the expected maxima characteristic of a vinyl group at 1630, 998, and 912 cm.$^{-1}$.

α-*Cyano*-1-*methyl*cyclo*hexylacetic Acid*.—A mixture of ethyl α-cyano-1-methyl*cyclo*hexylacetate (5 g.), concentrated hydrochloric acid (50 c.c.), and acetic acid (30 c.c.) was refluxed for 18 hr. Most of the solvent was removed under reduced pressure and the residue basified with sodium carbonate solution. A small amount of insoluble oil was removed with benzene, the aqueous solution acidified (4N-sulphuric acid), and the precipitated oil extracted with benzene. Drying (Na_2SO_4), removal of solvent, and distillation gave a highly viscous oil, b. p. 136—140°/0·15 mm., which slowly solidified. Crystallisation from light petroleum (b. p. 80—100°) gave α-*cyano*-1-*methyl*cyclo*hexylacetic acid* (3·2 g.; 74%) in needles, m. p. 75—77° (Found: C, 66·5; H, 8·2; N, 7·45. $C_{10}H_{15}O_2N$ requires C, 66·35; H, 8·35; N, 7·7%).

1-*Methyl*cyclo*hexylmalonamic Acid*.—Ethyl α-cyano-1-methyl*cyclo*hexylacetate (10 g.) was refluxed for 9 hr. with aqueous potassium hydroxide (16 g. in 32 c.c.). Water (50 c.c.) was then

added and the solution acidified with concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and crystallised from water; the amido-acid (4·75 g.; 50%) formed white plates, m. p. 151—153° (decomp.) (Robinson and Birch, *J.*, 1943, 501, give m. p. 151°).

1-*Methyl*cyclo*hexylglycine*.—A solution of 1-methyl*cyclo*hexylmalonamic acid (2·5 g.) in hot ethanol (25 c.c.) was added dropwise to a solution of hydrated barium hydroxide (23·8 g.) in water (1500 c.c.), and the solution stirred as the barium salt was precipitated. Bromine (0·75 c.c.) was carried into this suspension in a stream of nitrogen, and the mixture then heated by steam for 1 hr. The boiling solution was twice saturated with carbon dioxide and filtered, ammonium carbonate (7·25 g.) was then added, and the solution again heated to boiling and filtered. Concentration of the filtrate and cooling gave the amino-acid. 1-*Methyl*cyclo*hexylglycine* (1·85 g.; 85%) formed needles (from water), m. p. 205—207° (decomp.) (Found: C, 63·0; H, 9·85; N, 8·2. $C_9H_{17}O_2N$ requires C, 63·1; H, 10·0; N, 8·2%). The compound gave a strongly positive ninhydrin colour.

1-*Formyl*-1-*methyl*cyclo*hexane*.—(*a*) A solution of 1-methyl*cyclo*hexylglycine (1 g.) in 0·1N-sodium hydroxide (60 c.c.) was mixed with M-sodium hypochlorite solution (5·2 c.c.) and covered with ether (50 c.c.). The mixture was heated under reflux for 1 hr. Isolation by means of ether followed by distillation gave 1-*formyl*-1-*methyl*cyclo*hexane* (0·24 g.; 33%), b. p. 120°/546 mm., n_D^{21} 1·4490 (Found: C, 76·05; H, 10·9. $C_8H_{14}O$ requires C, 76·15; H, 11·2%). The 2:4-*dinitrophenylhydrazone* crystallised from ethanol as yellow needles, m. p. 154—155° (Found: C, 55·0; H, 5·9; N, 18·3. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%). Oxidation of the aldehyde with alkaline silver oxide furnished 1-methyl*cyclo*hexanecarboxylic acid, m. p. and mixed m. p. 37—38°.

(*b*) A mixture of freshly distilled dimethyl 1-methyl*cyclo*hexylmalonate (8 g.) and hydrazine hydrate (100%; 24 c.c.) was refluxed until a homogeneous solution resulted (3 hr.). The *dihydrazide*, which crystallised on cooling, was filtered off; it crystallised from ethanol in small needles (4 g.; 50%), m. p. 161—162° (Found: C, 52·5; H, 8·5; N, 24·35. $C_{10}H_{20}O_2N_4$ requires C, 52·6; H, 8·8; N, 24·55%).

Hydrogen chloride (0·68 g.) was passed into a mixture of the dihydrazide (2·1 g.), *n*-butyl nitrite (2·0 g.), and dry ethanol (5 c.c.), and the resulting solution set aside overnight. The mixture was refluxed for 9 hr., and the solvent then removed under reduced pressure. To the resulting crude diurethane 6N-sulphuric acid (10 c.c.) was added, and the mixture was steam-distilled. Ether extraction of the steam-distillate followed by distillation furnished 1-formyl-1-methyl*cyclo*hexane (0·44 g.; 45%), identical in all respects with the product obtained as in (*a*).

1-*Methyl*cyclo*hexylmalonamide*.—The preparation of *cyclo*hexylidenemalononitrile was carried out according to Cope and Hoyle's directions (*J. Amer. Chem. Soc.*, 1941, **63**, 733).

Addition of methylmagnesium iodide [from magnesium (8·85 g.)] to *cyclo*hexylidenemalononitrile (43·8 g.) was carried out as in the above cognate preparation of ethyl α-cyano-1-methyl-*cyclo*hexylacetate, yielding 1-*methyl*cyclo*hexylmalononitrile* (29 g.; 60%), b. p. 66°/0·1 mm., n_D^{16} 1·4715 (Found: C, 74·25; H, 8·25; N, 17·2. $C_{10}H_{14}N_2$ requires C, 74·05; H, 8·7; N, 17·3). The nitrile (14 g.) was heated under reflux with aqueous potassium hydroxide (11 g. in 60 c.c.) for 45 min. Cooling, filtration, washing with water, and crystallisation from ethanol yielded 1-*methyl*cyclo*hexylmalonamide* (8·5 g.; 50%) as plates, m. p. 264—265° (Found: C, 60·4; H, 8·45; N, 14·15. $C_{10}H_{18}O_2N_2$ requires C, 60·55; H, 9·15; N, 14·15%).

Hofmann Degradation of 1-*Methyl*cyclo*hexylmalonamide*.—Ice-cold bromine (18 g.) was added dropwise to a suspension of the amide (3·7 g.) in sodium methoxide solution (5·2 g. of sodium in 100 c.c. of methanol) at 0°. The resulting solution was heated by steam for 10 min., then acidified with acetic acid and evaporated to dryness under reduced pressure. Ethyl acetate extraction of the residue and removal of the solvent afforded an oily solid; crystallisation from ethanol gave the *hydantoin* of 1-methyl*cyclo*hexylglycine as needles, m. p. 228—230° (Found: C, 61·25; H, 7·95; N, 14·25. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2; N, 14·25%). Evaporation of the mother liquors from the above crystallisation gave an oil which was steam-distilled in the presence of sulphuric acid. Ether extraction of the steam-distillate gave a trace of an oil which furnished a yellow 2:4-dinitrophenylhydrazone, m. p. 154—155° after crystallisation from ethanol; the m. p. was unaffected by admixture with the corresponding derivative of 1-formyl-1-methyl*cyclo*hexane.

Hydrolysis of the hydantoin with aqueous barium hydroxide in an autoclave at 200° furnished 1-methyl*cyclo*hexylglycine, m. p. and mixed m. p. 205—207° (decomp.).

1-*Methoxycarbonyl*cyclo*hexylacetic acid*.—Treatment of 1-carboxy*cyclo*hexylacetic acid

(McRae and Lapworth, *loc. cit.*) with ethereal diazomethane afforded the *dimethyl ester*, b. p. 78°/0·5 mm., n_D^{19} 1·4621 (Found : C, 61·75; H, 8·2. $C_{11}H_{18}O_4$ requires C, 61·65; H, 8·45%).

A solution of this diester (9·52 g.) in 0·867N-methanolic potassium hydroxide (51·3 c.c.; 1 mol.) was refluxed for 3 hr. The solvent was removed under reduced pressure, water (50 c.c.) was added, and neutral component extracted with ether. Acidification with 6N-sulphuric acid, followed by isolation by means of ether, gave 1-*methoxycarbonyl*cyclo*hexylacetic acid* (6·64 g.; 75%) which crystallised from methanol in needles, m. p. 64—65° (Found : C, 60·05; H, 7·9. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%).

Methyl 1-*Bromomethyl*cyclo*hexanecarboxylate.*—Dry silver 1-methoxycarbonyl*cyclo*hexylacetate was prepared and converted into methyl 1-bromomethyl*cyclo*hexanecarboxylate by the process described for 1-bromomethyl-1-methyl*cyclo*hexane. The *ester* (60%) had b. p. 130°/35 mm., $n_D^{22\cdot5}$ 1·4845 (Found : C, 45·8; H, 6·6; Br, 33·8. $C_9H_{15}O_2Br$ requires C, 45·95; H, 6·45; Br, 34·0%).

1-*Methyl*cyclo*hexanecarboxylic Acid.*—(*a*) A solution of methyl 1-bromo*cyclo*hexanecarboxylate (1·5 g.) in acetic acid (40 c.c.) was treated with zinc dust (2 g.) and refluxed for 5 hr. After the acetic acid had been removed under reduced pressure, ether (50 c.c.) was added, and the ethereal extract was washed with sodium carbonate solution and water. Drying ($MgSO_4$) and distillation gave *methyl* 1-*methyl*cyclo*hexanecarboxylate* (0·5 g.; 51%), b. p. 70°/35 mm., $n_D^{18\cdot5}$ 1·4450 (Found : C, 69·0; H, 10·3. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The ester (0·5 g.) was heated with methanolic potassium hydroxide (0·9 g. in 10 c.c.) for 3 hr. Removal of solvent, acidification, isolation with ether, and distillation of the crude product gave 1-methyl*cyclo*hexanecarboxylic acid (0·31 g.; 68%), b. p. 234°, m. p. 38° undepressed on admixture with an authentic specimen. The corresponding amide crystallised in tiny needles, m. p. 68°, from ethyl acetate (Gutt, *Ber.*, 1907, **40**, 2069, gives m. p. 38—39° for the acid and m. p. 68—69° for the amide).

(*b*) To an ethereal solution of phenylmagnesium bromide [from magnesium (4·4 g.) and bromobenzene (38·2 g.)] was added methyl 1-methyl*cyclo*hexylacetate (14 g.) in an equal volume of ether, and the mixture was refluxed for 2·5 hr. The cooled mixture was poured into 6N-sulphuric acid and worked up as usual. The solvent was removed and the product heated to 200° for 30 min., cooled, and dissolved in ether. Drying, evaporation, and distillation gave 1-(2 : 2-*diphenylvinyl*)-1-*methyl*cyclo*hexane* (16·1 g.; 70%), b. p. 148°/0·5 mm., n_D^{17} 1·5861 (Found : C, 91·25; H, 8·5. $C_{21}H_{24}$ requires C, 91·25; H, 8·75%).

A solution of chromium trioxide (5·7 g.) in water (10 c.c.) was added during 10 min. to a vigorously stirred solution of this hydrocarbon (7·7 g.) in acetic acid (80 c.c.) at 60°. During the next hour more acetic acid (40 c.c.) and chromium trioxide (1 g.) were added and the mixture was stirred for a further 5 hr. at 60—70°. The acetic acid was removed under reduced pressure, 6N-sulphuric acid added, and the product extracted with benzene. Extraction with sodium carbonate solution, re-acidification, and isolation with ether and distillation gave a solid, m. p. 38° (1·87 g.; 47%) undepressed on admixture with an authentic sample of 1-methyl*cyclo*hexanecarboxylic acid.

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THE QUEEN'S UNIVERSITY, BELFAST.
THE UNIVERSITY, GLASGOW, W.2. [*Received, December 20th,* 1954.]

Photo- and Semi-conductance of Organic Crystals. Part I. Photo-effects in Tetracene and Anthracene.

By A. Bree, D. J. Carswell, and L. E. Lyons.

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Tetracene single crystals have been found to display a photoconductance effect in both the visible and the ultraviolet region. This effect, similar to that in anthracene, is promoted by the presence of air or oxygen, and removed by replacing the air with nitrogen. Thus it is concluded that the photoconductance is a surface phenomenon, in agreement with Lyons's theory to explain the spectral dependence. The photocurrent is in either crystal directly proportional to the applied field and also to the light intensity. Variations of current with time and with changed area of illumination are also reported. Naphthalene and phenanthrene gave no detectable currents under similar conditions to the others, and the theory is advanced that photoconductance varies with ease of aerial oxidation, increasing with ascent of the series naphthalene, anthracene, tetracene. Currents were found to be greater with tetracene than with anthracene.

Photoconductance in organic crystals is well known but no previous work has been performed on tetracene. Byk and Borck (*Ber. deut. phys. Ges.*, 1910, **8**, 621) and Volmer (*Ann. Physik*, 1913, **40**, 775) mention photoconductance in anthracene but the work in this period provided little knowledge of the actual processes involved. Since 1945 a number of workers have studied the photo- and semi-conductance of organic substances in the solid state, and in particular Szent-Györgyi (*Nature*, 1946, **157**, 857) has studied photocurrents in dyed proteins; Vartanyan (*J. Phys. Chem., U.S.S.R.*, 1946, **20**, 1065; *Acta Physicochim., U.R.S.S.*, 1947, **22**, 201; *Zhur. fiz. Khim.*, 1948, **22**, 770; 1950, **24**, 1361; 1953, **27**, 272; *Doklady Akad. Nauk S.S.S.R.*, 1950, **71**, 641) has examined semi- and photo-conductance in various dye molecules and mentions anthracene photoconductance, but we have found no detailed report of studies on anthracene. Nelson (*J. Chem. Phys.*, 1951, **19**, 798; 1952, **20**, 1327; 1954, **22**, 885) has confirmed and extended Vartanyan's work on dyes, and semiconductance in anthracene and certain other aromatic compounds has been observed by Eley (*Nature*, 1948, **162**, 819) and Eley, Parfitt, Perry, and Taysum (*Trans. Faraday Soc.*, 1953, **49**, 79) and by Mette and Pick (*Z. Physik*, 1953, **134**, 566) and Akamatu and Inokuchi (*J. Chem. Phys.*, 1950, **18**, 810). Preliminary reports of some of the work discussed in this series of papers have already appeared (Carswell, *J. Chem. Phys.*, 1953, **21**, 1890; Bree and Lyons, *ibid.*, 1954, **22**, 1630; Lyons, *ibid.*, in the press), and a suggestion that photo- and semi-conductance in anthracene-like crystals are closely related has been made by Carswell, Ferguson, and Lyons (*Nature*, 1954, **173**, 736). Since our first reports appeared the photoconductance of anthracene has been discussed by Chynoweth and Schneider and by Chynoweth (*J. Chem. Phys.*, 1954, **22**, 1021, 1029). However, the differences between their procedures and ours are considerable, and accordingly the results are to a large extent complementary. For example, we have worked with monochromatic light and studied the spectral distribution of the photoconductance: the Canadians have emphasised other features.

In the present experiments the crystals were prepared as thin sublimation flakes, and were mounted directly on to the electrodes and touched nothing else. The Canadians used much larger crystals, over 0·1" thick, and mounted them in "sandwich" and other cells with a supporting base for the crystal. Since the phenomenon is now known to involve surface effects, we feel it is valuable to have results from a variety of experimental procedures. A further difference between the Canadian work and ours is that we have examined the currents obtained at rather lower values of the electrical field applied across the crystal.

When this work was begun in 1950, existing results had all been obtained with polycrystalline materials, and mostly on substances for which neither phenomenon of light absorption nor the crystalline structure was well understood. This we judged to be a

handicap in understanding photoconductance. Although even now the spectrum of anthracene crystals has not been interpreted completely, yet a good deal is known about it (see Craig, *Rev. Pure Appl. Chem.*, **1953**, **3**, 207); since, in addition, the crystal structure of anthracene has been determined in detail (Robertson, " Organic Crystals and Molecules," Ithaca, New York, 1953), and also as anthracene has a considerable number of mobile electrons, it was chosen for the initial work. However, it will be shown that the phenomena observed and the techniques used are not confined to anthracene (*e.g.*, tetracene behaves very similarly) and the conclusions emerging from the work should often be transferable also to the dyes field.

The work has taken on a number of different aspects but, as the basic experimental methods were often constant, they are described for the most part in this first paper.

Experimental

The anthracene was first thoroughly purified by azeotropic distillation of 50 g. with 750 c.c. of ethylene glycol which had itself been purified previously. From the fraction of b. p. 197·5° anthracene was recovered by the addition of water. The process was repeated twice, and the final sample recrystallised from alcohol (m. p. 216°). Finally, to obtain the flakes used, sublimation was carried out from a well-lagged lipless 50-c.c. beaker covered with a perforated filter-paper and a crucible lid. Solid carbon dioxide was placed in the beaker some time before heating was commenced, in order to give a non-oxidising atmosphere. Fluorescence spectra, kindly taken by Mr. J. Ferguson, showed no trace of tetracene or other impurity. Certainly the purity was higher than that of a sample intended for use in a scintillation counter which was obtained and which had a yellow colour in a 1-cm. layer although fluorescing blue. The flakes obtained were frequently single crystals many of which showed interference colours. Any one crystal showed but a single colour which varied with the crystal thickness. The tetracene was obtained from a commercial sample, resublimed under nitrogen and spectroscopically free from other absorbing substances such as anthracene. Sublimed flakes were single crystals. Two methods of mounting were used: (*a*) The crystal was laid flat upon a silica disc with contacts made through " Aquadag " on the top surface; (*b*) the crystal was mounted between two platinum wire electrodes, spaced about 2 mm. apart. In both cases the electrode leads were held on a framework of stout copper wire mounted in a large rubber stopper which served as an insulating base. The whole of this electrode assembly was about 3" high and was portable. In (*b*) the crystal was attached to the platinum by means of a solution of " Aquadag," a suspension of carbon in water. The " Aquadag " as bought was diluted by about 1 : 1 and painted on the electrodes, after which the crystal was laid across the wires, and the whole allowed to dry. The crystal was now firmly attached to the wires, and the electrode assembly moved into position in a metal box where connections to the amplifier were made. This method of mounting, with the crystal surfaces not touching any supporting surface, except at the edges where the electrodes made contact, was chosen to avoid any possible electrical leak along the supporting surface and to ensure that any current that did not flow through the surrounding gas certainly did pass through the crystal itself. The light was incident on that side of the crystal to which the electrodes were connected.

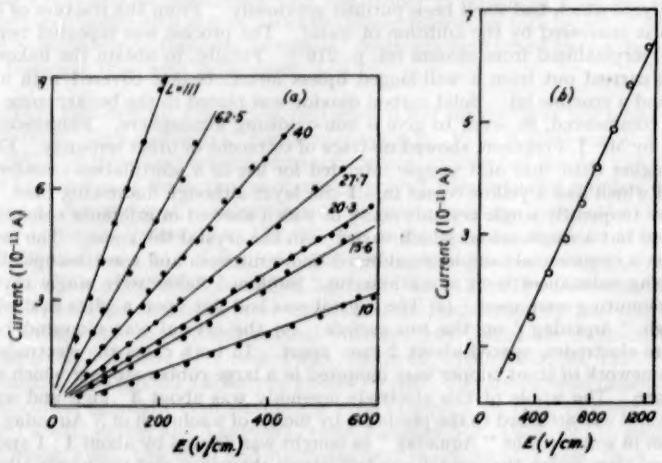
The metal box with two compartments was made to be screwed to the monochromator of a Beckman Spectrophotometer (Model DU). One compartment was so placed that the light beam entered it through a centrally positioned fused silica window; and in this compartment were placed the electrode assembly and a phosphoric oxide desiccant. Invariably before any measurements were taken both compartments were dried. The final adjustment of the crystal into the light beam was done visually after removal of the back of the compartment.

In the second compartment was the amplifier, so arranged that in the top of the box both current and voltage meters were visible. The amplifier used a single-stage triode electrometer valve, ME1401, with a 10^9, 10^{10}, 10^{11}, or 10^{12} ohm grid resistor. Full-scale deflection on the 50 μA meter was obtained with a current in the grid (10^{12} ohm) circuit of *ca.* 7×10^{-13}A. The sensitivity was linear. The amplifier had a time constant of about 20 sec. with the 10^{12} ohm but very much less with the 10^{10} ohm resistor. The dark current was *ca.* 10^{-14}A, or about one-tenth of a typical photocurrent. Before any reading, a zero adjustment was made by compensation of the dark current.

The atmosphere surrounding the crystal was air dried with phosphoricoxide. The lamps

used were the usual tungsten and hydrogen (300 ma) types supplied for the Beckman Spectrophotometer. These were used either in conjunction with the monochromator or with accompanying filters. The range of usefulness of the hydrogen lamp was confined to wavelengths above 2250 Å; at lower values the glass envelope did not transmit sufficiently to give appreciable currents. Above 3700 Å also the hydrogen-lamp emission curve showed maxima at 3790, 3875, and 4065 Å, minima at 3760, 3820, and 3915 Å (for a slit of 0·26 mm.). These intensity fluctuations were of the order of 5—10% of the average intensity over that wavelength range. Such considerations were important, since the first anthracene band system falls in the same range. Consequently, it was impossible to obtain a precise spectral dependence curve of the photoconductance without using two separate light sources. In taking an ordinary absorption spectrum the difficulty is not so important since it is then the ratio of incident to transmitted intensities which is of interest. With the photoconductance, however, one quantity of interest was the absolute value of the incident intensity; consequently, the best procedure is to determine the absolute output from each lamp at all wavelengths. The difficulties involved have so

Fig. 1. *Photo-current, I, plotted against electric field, E.*



(*a*) *Tetracene suspended between electrodes; tungsten lamp.* (*b*) *Anthracene on silica; hydrogen lamp.*

far prevented us doing this. But we have determined the relative intensities of light emitted at different wavelengths and this has enabled the recording of the results shown in Part II (following paper).

Flaws in the Crystal.—In some crystals flaws were clearly visible. Very often these had the effect of destroying all photoconductance phenomena, and so only crystals which appeared perfect were used.

Current–Applied Potential Relation.—As reported earlier for anthracene (Vartanyan; Carswell; Chynoweth and Schneider, *locc. cit.*) the current varies directly with the applied potential in the range studied. Results for anthracene, exemplified by Fig. 1, show that such a linearity holds from 0 to 1200 v/cm. for the particular light intensity used. The field strengths shown in this paper are calculated simply by dividing the applied voltage by the distance between the electrodes, the assumption being made that the drop in potential from one electrode to the other is steady and that there is no sudden change near either of the electrode surfaces which invalidates such a calculation. At one time (Carswell, *loc. cit.*) it was thought that there were signs of a plateau in the current–voltage curve before the current rose steadily again, but further work has shown that the curve is linear in the manner shown. The results of the various workers are accordingly in agreement. The values shown here are often accurate only to within about 15% because of the difficulties of measuring the separation of the "Aquadag" contacts.

Tetracene was investigated in some detail and the results are shown in Fig. 1*a*. Once again a rigorous linearity is obtained for constant light intensity. The various curves of the figure

demonstrate that simple proportionality holds for a wide variation in the incident intensity. The most obvious difference from the anthracene results is that the tetracene needs much lower voltages than anthracene to produce a given photocurrent. Alternatively the light intensity may be lower. This difference between the two compounds must be of importance in the final elucidation of the detailed mechanism and will be discussed later. The current–potential relation was of the same form with polychromatic light as with monochromatic.

The *current–light intensity relation* was studied in three different ways, depending on the method used to vary the light intensity. The results are shown in Fig. 2, *a* and *b*, for tetracene and anthracene, and it is seen that there is in all cases a simple proportionality between the current, I, and the light intensity, L. The three methods used to vary the light intensity were (*a*) moving the lamp from the crystal in measured steps; (*b*) inserting aluminised or silvered silica filters of known optical density; and (*c*) varying the slit on the Beckman spectrophotometer. In Fig. 2*a* a tungsten lamp of small filament size mounted behind an adjustable diaphragm was used, and the current with the lamp at the point of closest approach to the crystal is indicated by the encircled point at $L = 10$. The other circles indicate the

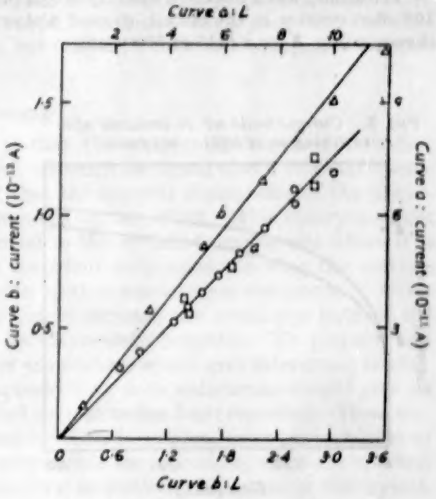


FIG. 2. *Photo-current, I, plotted against relative light intensity, L.*

○ *Intensity varied by moving lamp.*
□ *Intensity varied by inserting a silvered glass filter transmitting 55%.*
△ *Intensity varied by alteration of slit width and then moving lamp.*
(*a*) *Tetracene on silica, tungsten lamp,* (i) $E = 22$ v/cm.; (ii) $E = 60$ v/cm.
(*b*) *Anthracene suspended between electrodes,* $\lambda = 3900$ Å (*N.B.: change of L units*).

currents when the lamp was moved away from the crystal by a known amount. An inverse-square law was used to calculate the relative light intensity: thus with the lamp at $\sqrt{2}$ times its original distance $L = 5$. The linear relation so obtained was checked by a combination of methods (*a*) and (*b*), and the results are shown on the same graph by enclosing the points in squares. Method (*c*) allowed measurements to be made with monochromatic light. The slit of the Beckman spectrophotometer controls both entrance and exit beams and so, for a sufficiently wide and uniform beam, doubling the slit width gives a fourfold increase in the emergent light. This, in turn, if completely incident on the crystal, would give a fourfold increase in photocurrent. Experiments were conducted on both anthracene and tetracene in which the light did fall completely on the crystal even with the slit most widely open. In every instance the linear relation between L and I was confirmed, *e.g.*, see Fig. 2*b*.

The *current–time relation* for anthracene reported by Vartanyan (*loc. cit.*) was not accompanied by sufficient experimental detail to judge whether it is an effect due to the apparatus or to the crystal. The current build-up after turning on the light was reported to be about 30 sec. This result is in apparent disagreement with that of Chynoweth and Schneider (*loc. cit.*), where the build-up was apparently nearly instantaneous, being less than the constant of the input circuit of the amplifier used (10^{-1} sec.). However, these workers, on increasing the light intensity, suddenly observed a build-up of current over a period which seems to be of the order of a minute (no quantitative results are given in their Fig. 6). Such a result is obviously not attributable to the amplifier, but the complete explanation is not clear.

Superimposed upon these short-term variations the Canadians observed a relatively slow build-up over periods of up to 30 min. Also, with anthracene, Carswell (*loc. cit.*) reported a slow

build-up, but this was due largely to the circuit elements including the 10^{12} ohm grid resistor which was necessary to detect the feeble currents obtained with monochromatic light. This constant, defined as the time in which the current increased to 1/e of its maximum value, definitely depended on the circuit, being 20 sec. with the 10^{12} ohm resistor, 3 sec. with 10^{10} ohm, 1 sec. with 10^{9} ohm. The actual value depended, especially with the high resistances, upon the thoroughness with which the crystal had been dried. No sign of a decay from a quickly reached maximum was found except with one crystal, and this result could not be reproduced with other crystals. The particular mounting of the crystal and its previous history seem to make the results vary. With tetracene on a silica disc and with use of a 10^{10} ohm resistor the current meter came immediately to a steady value on every occasion. However, when current readings were recorded over several hours a very slow build-up of photocurrent was observed. At any point during this build-up, switching off the light caused the meter to read zero; re-illumination after a few seconds gave the same current as that measured before switching off. Thus the build-up was not due to some zero fluctuation but appeared to depend on a variation in the crystal condition which remained constant while the light was off for a few seconds.

Tetracene, when mounted directly across platinum electrodes with "Aquadag," and with a 10^{10} ohm resistor in the circuit, showed a slow build-up over 150 min., and typical curves are shown in Fig. 3 for a field of 500 v/cm.

FIG. 3. *Current build up in tetracene after switching on of light: two runs.*

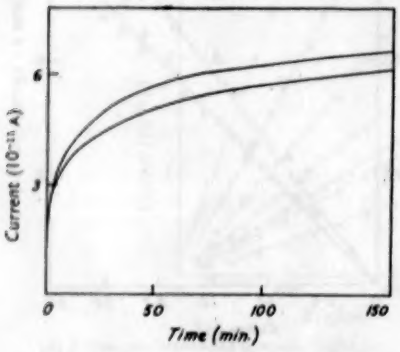
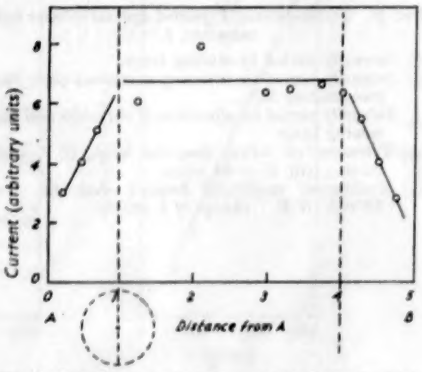


FIG. 4. *Effect of moving the light spot across the crystal from electrode A to electrode B.*



The broken lines mark the extremities beyond which only a portion of the light fell upon the crystal surface.
The circle indicates the size of the light spot.

The *effect of oxygen* on photoconductance of anthracene was discovered by Vartanyan (*loc. cit.*) and has been investigated by Chynoweth (*loc. cit.*). We have found that oxygen promotes photoconductance in tetracene, and have also obtained results in agreement with the other work on anthracene. Our early results on anthracene led us to test other substances including naphthalene and phenanthrene. Since there is a very close structural and spectroscopic similarity between these substances and anthracene it was thought that they too might show photoconducting properties. However, no current could be detected with either substance. Chemically, anthracene differs from the other two compounds in its much greater readiness to form a quinone upon oxidation. Sublimation of anthracene must be carried out in a non-oxidising atmosphere to prevent aerial oxidation (in this work, carbon dioxide was used), whereas the others may safely be sublimed in air. Consequently, it was thought that photoconductance and ease of oxidation might be linked. In order to test this hypothesis tetracene was examined, since its ease of oxidation is known to be greater than that of anthracene. As pointed out above, the photoconductance of tetracene is greater than that of anthracene at similar values of field and light intensity. It was accordingly stated by Bree and Lyons (*loc. cit.*) that photoconductance increases as the series naphthalene, anthracene, tetracene is ascended. This lays a basis for future work on the higher members of the series. It now seems that photoconductance in organic crystals is to be expected when there is the possibility of a combination with oxygen.

Such a combination need not be the complete formation of a quinone but could be some intermediate such as is formed by an association of the triplet oxygen molecule with the hydrocarbon molecular centre, itself possibly in a triplet state such as has been thought to occur in semiconduction (Part II, *loc. cit.*; cf. Bowen, *Discuss. Faraday Soc.*, **1953**, **14**, **143**; Carswell, Ph.D. Thesis, Sydney, **1954**). Some such intermediate from anthracene has been postulated independently by Chynoweth (*loc. cit.*). Our results showed that on replacement of the oxygen atmosphere by an inert gas such as nitrogen or by a vacuum the photocurrent decreased, and *vice versa*, the process being reversible. It follows that the intermediate was not the quinone itself, which would be stable in air.

The effect of changing the area of illumination was studied by moving a small light spot across the crystal from one electrode, *A*, to another, *B*. The results are shown in Fig. 4. Where the light fell partly on to the " Aquadag " contact the current was reduced, but where the whole light fell upon the anthracene crystal it is seen that the current was independent of the position of the beam between the electrodes.

Irradiation in the infrared after switching off the ultraviolet source gave no measurable current increase, emphasising a difference in mechanism from certain inorganic photo-conductors. One crystal, exceptionally sensitive to the ultraviolet, was found which gave currents when irradiated with infrared of wavelength about 3 μ, but this result could not be repeated on other crystals.

Discussion

Possibly the most important conclusion is that the photoconductance is a surface phenomenon, as Chynoweth has also concluded, although he found also a residual photoconductance *in vacuo*. Lyons (*loc. cit.*) found that the spectral dependence of the photoconductance can be explained if the phenomenon is a surface effect. This theory assumes that energy as an " exciton " must be transferred to the surface from the site where it is absorbed and becomes effective in producing a current only upon reaching the surface, since it is the surface layer which contains an anthracene–oxygen compound. Alternatively, the oxygen compound could be thought to increase the mean free path of the electrons and so increase the photocurrent, as Chynoweth suggests. To prepare and examine anthracene in a completely oxygen-free atmosphere would give interesting results, for if the carriers originate in the oxygen compound then such anthracene should give no current at all, and not merely a greatly decreased current as has been reported. However, if the carriers do not need an oxygen compound for their formation, some perturbation of the crystal field in the surface layer must be responsible for ionisation, since the spectral properties of anthracene do not indicate that internal ionisation takes place in the crystal. In a molecular crystal such as anthracene the intermolecular forces are small (Davydov, *Izvest. Akad. Nauk, S.S.S.R.*, **1950**, **14**, 502), and so there should be no large change in the properties of molecules on the surface compared with those in the bulk. Accordingly, ionisation should not be expected in the surface if it does not take place in the bulk. Hence we conclude tentatively that the current carriers are formed by the transfer of energy to the anthracene–oxygen compound [unless some effect at the electrode boundary is the cause of ionisation, but there is no evidence at all for this: indeed, the constancy of the photocurrent with varying position of illumination shown in Fig. 4 is evidence of an opposed kind (cf. Chynoweth, *loc. cit.*)].

We are glad to acknowledge the help given by the Vacuum Oil Co. for a scholarship (to D. J. C.) and by the Commonwealth Research Fund for equipment and the support (of A. B.). Dr. T. Iredale gave kindly encouragement in the early stages of the work.

University of Sydney, Australia. [*Received, December 22nd*, 1954.]

Photo- and Semi-conductance of Organic Crystals. Part II. Spectral Dependence, Quantum Efficiency, and a Relation between Semi- and Photo-effects in Anthracene.*

By D. J. Carswell and L. E. Lyons.

[Reprint Order No. 5994.]

Photoconductance in anthracene displays a spectral dependence which reproduces the maxima and minima of the ultraviolet absorption spectrum of the crystal. Such a dependence may be explained by the necessary participation of surface molecules to which absorbed energy must be transferred as excitons. There is a separate threshold of photoconductance for each electronic transition. The position of the transition to a molecular triplet level coincides with the activation energy determined by others for semiconductance. The quantum efficiency of photoconductance depends upon the applied field and is of the order of 10^{-4}. The introduction of 10^{-4}M-tetracene into anthracene increases the photocurrents, especially in the region of the second electronic transition (40,000 cm.$^{-1}$).

The wavelength dependence of the photoconductance of anthracene has not been previously reported except in a preliminary way in connection with the present work. The threshold of photoconductance was found by Volmer to occur at about 4000 Å, and as this has been confirmed by Vartanyan (references in Part I *) and with considerable accompanying detail by us, it may be assumed that other values sometimes reported are in error. As is now shown, to talk of a simple threshold is not by any means a sufficient description of the phenomenon, since it is not true that light of all wavelengths below the "threshold" is equally effective in promoting photoconductance. This is true even if "threshold wavelength" were always perfectly defined. The term has been used to denote the wavelength at which a current either is just detectable or else reaches half its maximum value. The latter usage, although precise, refers to a quantity which varies with the experimental conditions. A better definition than either, if the term is retained, is the wavelength at which the current first reaches a maximum value, a usage analogous to that of $\lambda_{max.}$ in absorption spectroscopy. With anthracene and similar molecules, photoconductance is related closely to the absorption spectrum of the crystal and such an analogy is accordingly justified. We have suggested a rule (Carswell, Ferguson, and Lyons, *Nature*, **1954**, **173**, 736) that wavelengths locating an electronic transition are those which give rise to photoconductance, and furthermore, that to every electronic transition of the vapour molecule there corresponds a region of photoconductance in the crystal. Evidence presented below is consistent with this rule, as is a more recent study on tetracene (Bree and Lyons, *J. Chem. Phys.*, **1954**, **22**, **1610**).

Experimental

A Beckman spectrophotometer (stripped of its photocell attachment and fitted with the specially made photoconductance cell and amplifier attachment as described in Part I, *loc. cit.*) was used as a monochromator in conjunction with the usual tungsten and 300-mA hydrogen discharge lamps. For the experiments with polarised radiation a piece of "Polaroid" was used, after its spectrum had shown it to be a perfectly satisfactory polariser for light in the anthracene long-wave absorption region; in such experiments a monochromator was not used but was replaced by a mercury-discharge lamp plus a filter to transmit the 3650 Å region. The exact transmission was checked spectrally and found to extend over about 700 Å. Complete "spectra" have since been obtained by Bree and Lyons (*loc. cit.*), using polarised radiation and a photoconductance method. In all the above-mentioned experiments a single crystal was suspended between two platinum electrodes and attached with "Aquadag," but in order to examine the optical directions in the crystal it was necessary to mount the crystal on a removable glass piece to which "Aquadag" contacts were made; the illumination was now through the glass. Markings on the glass were made to indicate directions of maximum and minimum current

* Part I, preceding paper.

when plane-polarised light was used, and these were then correlated with optical directions with the aid of a polarising microscope. With a glass mount, somewhat unstable dark currents were introduced, and so there were now included a more intense light source and a less sensitive amplifier incorporating a ME1400 electrometer valve and a 10^{10} ohm grid resistor. In this way fluctuations in the dark current became of reduced importance.

The quantum efficiency of photoconductance, *i.e.*, the number of electrons entering the external circuit for each quantum of radiation absorbed, was determined with sufficient accuracy to ensure that the result was correct to within a power of ten. A new 931A photomultiplier tube with stabilised high-tension supply was used as a measuring device, and use was made of the manufacturer's published sensitivity characteristics : at 4000 Å, 1395; 3650 Å, 1316 μA/μW. The apparatus was set up as in Fig. 1 so that a narrow cone of nearly monochromatic (3650 Å) light was focused on to the crystal between the electrodes and the emergent light, collected by a large-aperture lens, and allowed to fall on the photocathode. With this arrangement it was shown that only a negligible amount of light penetrated an absorption band of the crystal. A small fraction, 2%, of the incident light intensity did indeed emerge from the crystal. This was

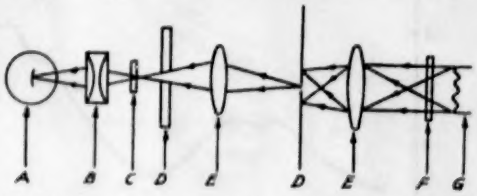


FIG. 1. *Arrangement used for determining quantum yield.*
A, photomultiplier.
B, wide-aperture lens.
C, crystal.
D, screens with small openings.
E, lens.
F, filter.
G, lamp.

attributed largely to fluorescence and so the intensity of the incident beam (measured with the crystal removed) was taken to give a satisfactory measure of the light absorbed. The photocurrent was measured with a field of about 600 v/cm.

RESULTS AND DISCUSSION

The spectral dependence of the photocurrent, which may be studied in several ways, depends on the variation of slit width with wavelength. In the Beckman spectrophotometer the entrance and exit slits work together so that doubling the slit width gives, for sufficiently narrow widths, a quadrupling of the emergent intensity. The simplest method to determine the spectral dependence is with a constant slit width, but in addition either a constant wavelength interval or a constant wave-number (*i.e.*, frequency) interval may be used. All three methods were used and the results are shown in Fig. 2, labelled (*a*), (*b*), and (*c*), respectively. The wave-numbers of the maxima show that in each case there is a close

Frequencies $\bar{\nu}$ *(cm.*$^{-1}$*) and wavelengths* λ *(Å) of maxima.*

Photoconductance of crystal		Absorption spectrum of crystal		of solution in *iso*octane	
λ	$\bar{\nu}$	$\bar{\nu}$ [1]	$\bar{\nu}$ [2]	$\bar{\nu}$ [3]	$\bar{\nu} - 1040$ †
First transition					
3915	25,550	25,580	25,540	26,640	25,600
3800 *	26,320	—	—	—	—
3700	27,030	27,030	26,990	28,090	27,050
3530	28,330	28,490	—	29,560	28,460
3420	29,240	—	—	—	—
3310	30,210	29,850	—	30,860	29,820
3140	31,850	—	—	—	—
3060	32,680	—	—	—	—
2960	33,780	—	—	—	—
Second transition					$\bar{\nu} - 2250$
2685	37,240	—	37,520	39,840	37,590
2590	38,610	—	—	—	38,570
2495	40,080	—	—	—	—
2370	42,190	—	43,480	—	—

[1] Kortum and Finckh, *Z. physikal. Chem.*, 1952, **52**, *B*, 263. [2] Craig and Hobbins, *J.*, 1955, 539.
[3] Catalog of Ultraviolet Spectrograms, A.P.I. Project 44 at N.B.S. * Probably due to a hydrogen line.
† Values corrected by the amounts shown for the shift upon change of phase.

resemblance to the ordinary absorption spectrum of the crystal. The correspondence is shown clearly in Table 1 and is seen to apply not only to the first (low-energy) transition beginning at about 25,500 cm.$^{-1}$, but also to the second transition at about 37,240 cm.$^{-1}$. The greater amount of structure in (*b*) than in (*a*) is due to the use of a smaller slit width in (*b*), 0·13 mm. at 23,810 cm.$^{-1}$ compared with 2·0 mm. Since the curves were taken with a hydrogen lamp which emitted lines, there was the danger of recording false maxima in the photoconductance results although not to an equal extent in the absorption spectra, for the reasons discussed in Part I (*loc. cit.*). One maximum believed to be false is marked with an asterisk in the Table; it has no analogue in the absorption spectrum. The most pronounced maxima in the photoconductance curves occur at wavelengths which are in bold type in the Table. All of these have some recorded analogue in the absorption spectra. Of

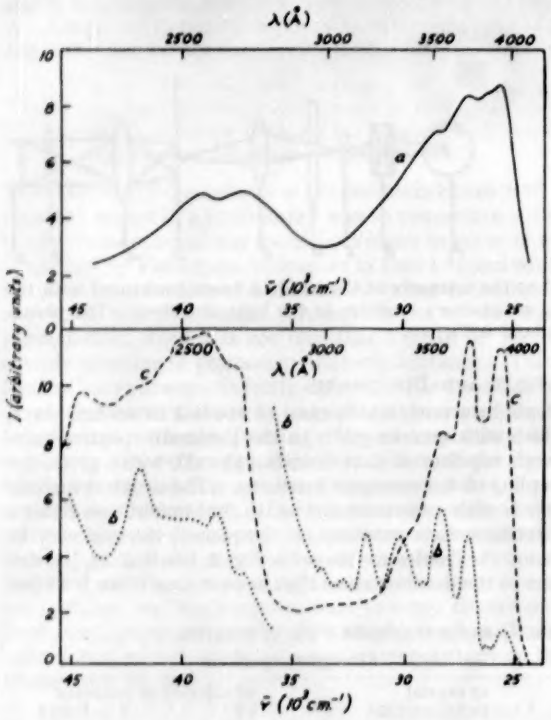


FIG. 2. *Observed spectral dependence of the photocurrent in anthracene crystals in air.*
(*a*) *With a constant* (2 *mm.*) *monochromator slit width.*
(*b*) *With slit giving a constant* $\Delta\lambda$ (25 Å) *on to crystal.*
(*c*) *With slit giving a constant* $\Delta\tilde{\nu}$ (750 *cm.*$^{-1}$) *on to crystal.*

the maxima which are less pronounced in the photoconductance curves (in ordinary type in the Table) a number have no analogues in the absorption spectra, but, since there are no known hydrogen lines at the measured wave-numbers, there is no reason to doubt the genuineness of the maxima. Consequently, the photoconductance method is seen to supply information which supplements that already obtained by the more usual methods of absorption spectroscopy. Errors in the determination of the bold-face wavelengths might amount to ± 5 Å (± 40 cm.$^{-1}$) whilst errors in the other wavelengths might be somewhat greater.

The magnitude of the current at different wave-numbers is of considerable interest. The main conclusion from the curves in Fig. 2 is that the current is greatest in the two regions where the crystal absorbs, and falls to a minimum between the absorbing regions. This is true of all three curves (*a*), (*b*), and (*c*) but is more easily seen in (*a*) and (*c*) than in (*b*). Whilst curves (*a*) and (*c*) are actual experimental curves, each made on a particular crystal, it proved impossible to obtain a curve of type (*b*) with a single crystal, owing to the great increase of current at the higher wave-numbers which resulted from the necessary 14-fold

increase in slit width. In Fig. 2(*b*) the curve is composite, the part at lower wave-numbers being recorded under different conditions from that at higher. The effect of this is to reduce the height of the higher wave-number part relatively to the remainder. Comparison of the magnitudes of I at different wave-numbers is not a simple matter unless either the difference in the I values is very great or that in the wave-number values is small. There is no

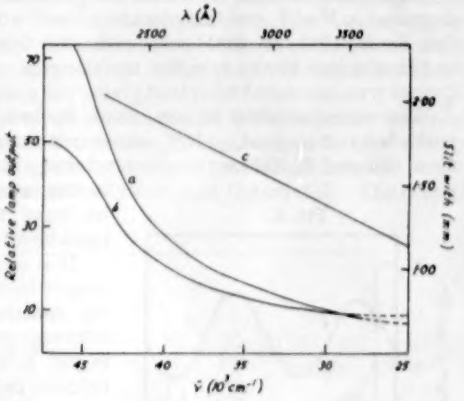


FIG. 3. *Variation in hydrogen lamp relative output with wave-number; and variation in slit to give a constant* $\Delta\tilde{\nu} = 750$ *cm.*$^{-1}$.
(*a*) *Lamp energy output.*
(*b*) *Lamp quantal output.*
(*c*) *Slit width.*

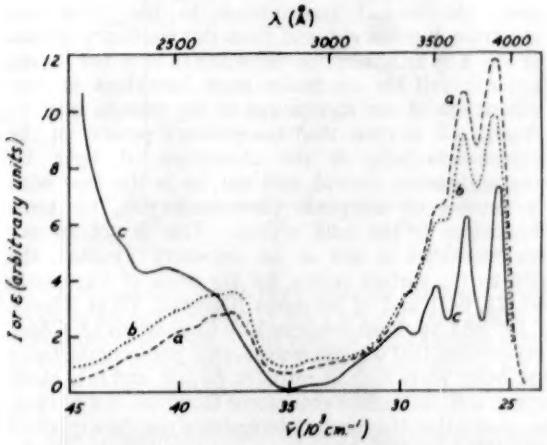


FIG. 4. *Curve* (*c*) *of* FIG. 2 *corrected for entrance slit variation with wave-number.*
(*a*) *Constant energy incident on crystal.*
(*b*) *Constant number of quanta incident.*
(*c*) *Absorption spectrum of crystal.*

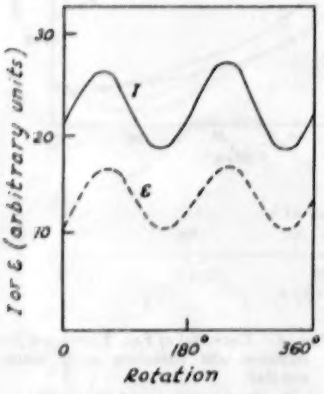
doubt from Fig. 2 that there is a general resemblance to the crystal absorption spectrum, or that I at a peak is greater than I at immediately neighbouring wave-numbers. But it is not at all clear whether I reaches a greater value in the first absorption region or in the second. Such comparison of I values at widely differing wave-numbers is improved if the curves are corrected first for the variation in the output of the lamp with wave-number, and secondly, for the alteration in the entrance slit with wave-number. The second correction is not necessary with curve (*a*), since both the entrance and exit slits of the monochromator were held constant. The first correction may be made in one of two ways depending on whether a curve is desired which represents a constant quantal output or a constant energy output from the lamp. (By constant quantal output is meant that the number of quanta at the entrance slit is constant with wave-number.) Allowance must also be made where necessary either for the varying dispersion of the monochromator or for variation in the exit slit.

Two curves, shown in Fig. 4, are of considerable significance: (i) curve 2(*c*) corrected first to give a constant entrance slit and secondly to give a constant energy output from the

lamp, and (ii) curve 2(*c*) corrected to give constant entrance slit and constant quantal output from the lamp. Fig. 3 shows curves used in making the corrections and gives the lamp output as a function of wave-number as well as the variation in exit slit necessary to pass a constant band of $\Delta\bar{\nu} = 750$ cm.$^{-1}$. The lamp-output curve, which is not in absolute units, is based upon the maker's curve for a Hilger–Flood lamp similar to the lamp actually used. Extrapolation without regard to the presence of hydrogen lines, the effect of which was discussed in Part I, was done in accordance with Allen's curve for a hydrogen arc (*J. Opt. Soc. Amer.*, 1941, **31**, 2681) and can be very little in error, since the curve is almost parallel to the abscissa at the relevant wavelengths. The curve giving the relative numbers of quanta was calculated from that giving the energy.

The reproducibility of, say, curve 2(*c*) was excellent as regards wave-number of the peaks but not so good, $\pm 15\%$, as regards the ratio of the currents under given conditions at 40,000 and 27,030 cm.$^{-1}$. Such accuracy is comparable, however, with that obtainable in the measurement of crystal absorption spectra, as we have found. The accuracy may therefore be considered satisfactory at present.

FIG. 5.



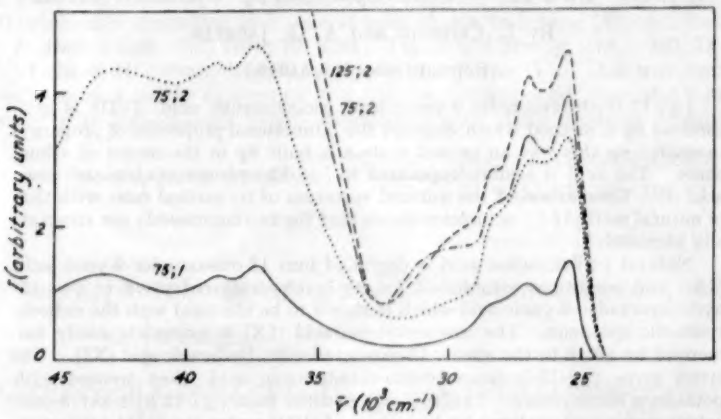
It is seen that removal of variation over the spectral range which was due to the lamp emission, the entrance slit, and the monochromator dispersion makes a great difference to the curve in Fig. 2(*c*). Curves (*a*) and (*b*) in Fig. 4, which result, are alike in showing a greatly reduced current in the higher energy system. However, the overall resemblance to the absorption spectrum is preserved, and from this similarity (shown in Fig. 4 by an absorption curve due to Bree and Lyons, unpublished) the conclusion most important in considerations of the mechanism of the process may be drawn. It is clear that the primary process in the photoconductance is the absorption of light by the anthracene crystal, and not, as is the case with a number of inorganic photoconductors, by some impurities in the bulk crystal. This is not to say that the presence of non-anthracene molecules is not at all necessary; indeed, the opposite is the case at least in regard to the surface layers, for the work of Vartanyan (*Doklady Akad. Nauk S.S.S.R.*, 1950, **71**, 641) and of ourselves (Carswell, Ph.D. Thesis, University of Sydney, 1954; Part I, *loc. cit.*) has been confirmed by Chynoweth (*J. Chem. Phys.*, 1954, **22**, 1029), and it is now established that oxygen increases the photoconductance above its vacuum value in a way that other gases such as nitrogen do not, and it is likely that some compound between the oxygen and the surface anthracene facilitates the process. Lyons (*J. Chem. Phys.*, in the press) has shown that the spectral dependence may be explained upon the assumption that exciton migration from the absorption site to the surface is the necessary second step in the mechanism. The following steps, however, are very much less clear. The possibility of ionisation of the surface anthracene is hard to determine but certainly must be considered in the absorption region if the effective dielectric constant is anything like the macroscopic value. However, it is plain that it is necessary first to produce an excited electronic state of the anthracene in the crystal surface. There is some evidence (Carswell, Ferguson, and Lyons, *loc. cit.*) that not only states corresponding to singlet excited states in the vapour but also those corresponding to triplet excited states are effective in giving rise to conduction. In this way a connection has been seen between photo- and semi-conduction. It is therefore of interest to compare the relevant energy quantities: Eley, Parfitt, Parry, and Taysum (*Trans. Faraday Soc.*, 1953, **49**, 79) and Mette and Pick (*Z. Physik*, 1953, **134**, 566) are in agreement that the activation energy of semiconductance in anthracene crystals is 1·65 ev (13,400 cm.$^{-1}$). This is interpretable if it corresponds to the height of the first "triplet" level above the ground state, 14,700 cm.$^{-1}$ in the vapour (Kasha and McGlynn, *Ohio State University Symposium on Molecular Structure and Spectroscopy*, June, 1954). Experimental work on photoconduction is difficult in this region, but on the above theory there

should be a very weak photoconductance effect produced by very near infrared radiation. One "threshold" of photoconduction would accordingly be in the infrared region at a much lower energy than that of the threshold observed by us at 25,550 cm.$^{-1}$ (3915 Å) if the maximum is taken, or at about 24,400 cm.$^{-1}$ (4100 Å) if the point of first current detection is taken.

At wave-numbers above 37,000 cm.$^{-1}$ the resemblance between photoconductance curve and absorption spectrum apparently ceases. This could conceivably be due to some experimental failure in the region, which is the most difficult of all to work in, or else could mean that some modification to the simple theory is necessary. This point is being investigated further.

A further point of similarity between photoconductance and the absorption spectrum was found in the effect of linearly polarising the radiation incident upon the crystal. As the plane of polarisation of the radiation was rotated, the current varied as shown in Fig. 5, in which also is shown the variation in extinction coefficient, ε, of the crystal. The crystal

FIG. 6.



direction coinciding with the maximum value of I was determined by the polarising microscope to be exactly that of the b crystal axis, which is known to be also the direction for maximum absorption. The ratio of I due to light with the electric vector vibrating parallel to b to that perpendicular to b was determined as 1·5 : 1, in good agreement with the ratio of absorption coefficients 1·8 : 1 (Bree and Lyons, unpublished; Craig and Hobbins, *loc. cit.*).

The absolute quantum efficiency was not expected to be very high in view of the fact that for anthracene crystals the quantum yield of fluorescence is about 0·9 (Bowen, *Trans. Faraday Soc.*, 1939, **35**, 15). These determinations were in agreement in showing that at 3650 Å almost 10,000 quanta were necessary to produce one electron in the external circuit. Obviously, most absorbed energy is re-emitted. The quantum efficiency varies directly with the applied field, as was shown in Part I, and this figure gives only the order of magnitude at a field of approximately 600 v/cm.

Mixed Crystals.—Since in many inorganic substances the introduction of impurities is able to modify the photoconductance, tetracene was deliberately introduced into anthracene in a way similar to that used by Lipsett and Dekker for other studies (*Canad. J. Phys.*, 1952, **30**, 165). At concentrations above about 10^{-3}M tetracene ceases to form a solid solution and forms separate layers in the "crystal." The lower concentrations which were necessary to maintain homogeneity have so far prevented us from examining any photoconductance arising from absorption by the tetracene below 25,000 cm.$^{-1}$. The curves shown in Fig. 6 are the result of absorption by the anthracene and maintain a resemblance to the results on the tetracene-free samples. However, currents are greater in the higher

than in the lower energy region when tetracene is present, as can be seen by comparing Fig. 6 with 2(*a*). With pure tetracene, currents are much higher than with pure anthracene (Bree and Lyons, *loc. cit.*), and this is consistent with the increased current in the mixed crystal arising from the relatively few tetracene molecules present. Some crystals gave exceptionally large and unstable currents in the higher energy region, and in all cases in both regions smaller potentials than with pure anthracene gave rise to instability.

The Vacuum Oil Co. and the Commonwealth Research Fund are again to be thanked, as is Mr. Bree for checking certain of the results and for allowing us to reproduce the absorption spectrum of anthracene crystals, and Mr. Ferguson for unpublished information on anthracene crystals containing tetracene in concentration greater than 10^{-3}M.

UNIVERSITY OF SYDNEY, AUSTRALIA. [*Received, December 22nd,* 1954.]

Lipids. Part II. Total Synthesis of Ricinoleic Acid.*

By L. CROMBIE and A. G. JACKLIN.

[Reprint Order No. 51016.]

(±)-12-Hydroxyoctadec-9-ynoic acid (ricinstearolic acid) (VII) is synthesised by a method which employs the bifunctional properties of propargyl bromide: in this way an yn-β-ol system is built up in the centre of a long chain. The acid is semihydrogenated to (±)-12-hydroxyoctadec-*cis*-9-enoic acid (I). Comparison of the infrared spectrum of its methyl ester with that of natural methyl (+)-ricinoleate shows that the two compounds are structurally identical.

Natural (+)-ricinoleic acid is degraded into 12-oxo-octadec-9-ynoic acid (IX), and conditions established for its borohydride reduction to (±)-12-hydroxyoctadec-9-ynoic acid which is shown to be identical with the entirely synthetic specimen. The oxo-acetylenic acid (IX) is extremely easily isomerised by alkali to the allenic 12-oxo-octadec-9 : 10-dienoic acid (XI). The latter gives (±)-12-hydroxy-10-oxo-octadecanoic acid when treated with potassium borohydride. This is shown to differ from (±)-12-hydroxy-9-oxo-octadecanoic acid, isolated by hydration of (VII) under the usual acidic conditions, and an explanation for its formation is proposed.

Since ricinstearolic acid can be converted into ximenynic acid, a total synthesis of the latter is also achieved.

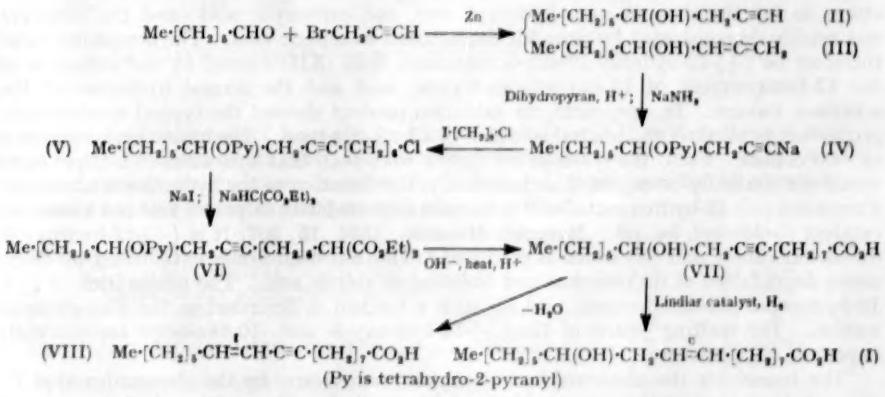
(+)-RICINOLEIC ACID (I) is the main fatty acid in castor oil, which is obtained from the seeds of *Ricinus communis* (family Euphorbiaceae). A recent report (Hilditch and Riley, *J. Sci. Food Agric.*, **1951**, **2**, 245) states that on hydrolysis the glycerides yield 91·4—94·9% of this, together with 4·5—5·0% of linoleic acid and small amounts of oleic, saturated, and dihydroxy-acids. The natural occurrence of the acid is discussed by Hilditch (" Chemical Constitution of Natural Fats," Chapman and Hall, London, 1947, p. 170), Ralston (" Fatty Acids and Their Derivatives," Wiley, New York, 1948, p. 188), and Eckey ("Vegetable Fats and Oils," Reinhold, New York, 1954, p. 587). Saalmuller (*Annalen*, **1847**, **64**, 108) appears to have been the first to isolate ricinoleic acid in moderately pure form and after Krafft's proposal (*Ber.*, **1888**, **21**, 2730) that it was 12-hydroxyoctadec-10-enoic acid, the correct structure was shown to be 12-hydroxyoctadec-9-enoic acid by Goldsobel (*Ber.*, **1894**, **27**, 3121; cf. Baruch, *Ber.*, **1893**, **26**, 1867; **1894**, **27**, 172, 176; Holt and Baruch, *Ber.*, **1893**, **26**, 838). Goldsobel's structure is supported by a considerable body of later evidence. The present communication reports the first total synthesis of (±)-ricinoleic acid (for a summary see *Chem. and Ind.*, **1954**, 1197).

n-Heptaldehyde was converted, either by a Reformatski reaction employing zinc and propargyl bromide (cf. Ziele and Meyer, *Ber.*, **1942**, **75**, 356; Henbest, Jones, and Walls,

* The paper by Crombie and Taylor (*J.*, 1954, 2816) is considered to be Part I of this series.

J., 1949, 2696; Crombie, *J.*, 1955, 1007) or, less well, by a Grignard reaction with propargylmagnesium bromide (Golse and Le-Van-Thoi, *Compt. rend.*, 1950, **230**, 210; Prevost, Gaudemar, and Honigberg, *ibid.*, 1950, **230**, 1186; Gaudemar, *ibid.*, 1951, **233**, 64) into (±)-4-hydroxydec-1-yne (II). In view of reports (Wotiz, *J. Amer. Chem. Soc.*, 1951, **73**, 693; Celmer and Solomons, *ibid.*, 1953, **75**, 3430) it seemed likely that the dec-1-yne (II) would be contaminated by the allene (III) and presence of the latter was demonstrated in the product from the Reformatski reaction by the characteristic infrared absorption at *ca.* 1970 cm.$^{-1}$ (Sheppard and Simpson, *Quart. Rev.*, 1952, **6**, 1; Wotiz and Celmer, *J. Amer. Chem. Soc.*, 1952, **74**, 1860). The allene does not interfere with subsequent stages in the synthesis because, when the mixture is converted into the tetrahydropyranyl ether (Parham and Anderson, *ibid.*, 1948, **70**, 4187) and then treated with sodamide in liquid ammonia, only the decyne (II) gives a sodio-derivative (IV). It is conceivable that isomerisation of the allene to the acetylene proceeds under the influence of sodamide but we have no experimental evidence on this point: Bouis [*Ann. Chim.* (*France*), 1928, **9**, 459] describes such rearrangements under more drastic conditions.

The sodio-derivative of (±)-4-(tetrahydropyranyloxy)dec-1-yne was treated with 1-chloro-6-iodohexane according to a general method due to Strong (Ahmad, Bumpus, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 3391; Taylor and Strong, *ibid.*, 1950, **72**, 4263), to give (±)-1-chloro-10-(tetrahydropyranyloxy)hexadec-7-yne (V). This was heated under reflux with sodium iodide in acetone and the 1-iodo-compound, formed by metathesis, was treated with sodiomalonic ester. Hydrolysis with alkali, thermal decarboxylation,



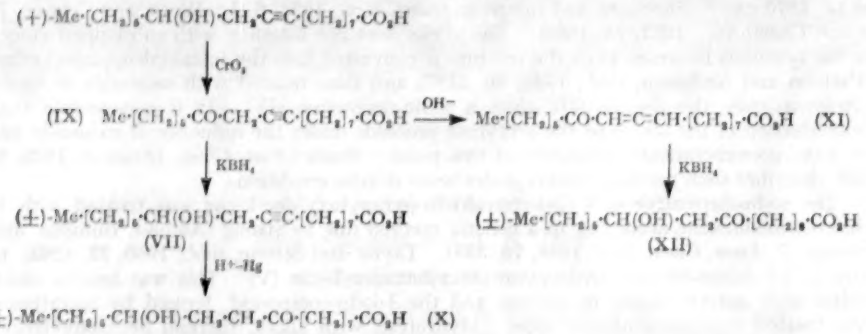
(Py is tetrahydro-2-pyranyl)

and destruction of the pyranyl residue in acid produced (±)-12-hydroxyoctadec-9-ynoic acid [(±)-ricinstearolic acid (VII)]. This was obtained crystalline, m. p. 53—53·5°, and characterised as its *p*-bromophenacyl ester.

Before proceeding further it seemed desirable to degrade natural (+)-ricinoleic acid to (±)-ricinstearolic acid and rigidly confirm the identity of the synthetic specimen by direct comparison. Natural (+)-ricinoleic acid was brominated and dehydrobrominated to give (+)-ricinstearolic acid (Ulrich, *Z. fur Chemie*, 1867, **3**, 545; Grün and Woldenburg, *J. Amer. Chem. Soc.*, 1909, **31**, 490). Oxidation with chromic acid at 0° then gave 12-oxo-octadec-9-ynoic acid (IX) in satisfactory yield, hydrogenated to 12-oxo-octadecanoic acid as expected (mixed m. p.). It is important that no trace of alkali is used during the working up of the oxo-acetylenic acid for reasons discussed below. When the acid (IX) was reduced with an excess of potassium borohydride in 90% methanol at 0° and then decomposed with dilute sodium hydroxide at 45°, the required (±)-12-hydroxyoctadec-9-ynoic acid (VII) was obtained in 85% yield. It was identical in all respects with the acid produced by total synthesis.

The correct conditions for reductionof the acetylenic ketone (IX) to the acetylenic alcohol (VII) were only arrived at after considerable experimentation. 12-Oxo-octadec-9-ynoic acid,

when neutralised to phenolphthalein and then treated, in aqueous solution, with potassium borohydride, gave oils. Reduction in methanol or methanol containing a little water gave a crystalline substance, m. p. 82°, in yields of up to 40%, after the product had been decomposed with alkali in the usual way : this was different from (±)-12-hydroxyoctadec-9-ynoic acid; its empirical formula was $C_{18}H_{34}O_4$ and it yielded a *p*-bromophenacyl ester, a semicarbazone, and a 1-naphthylurethane, all crystalline. This utilises the four oxygen

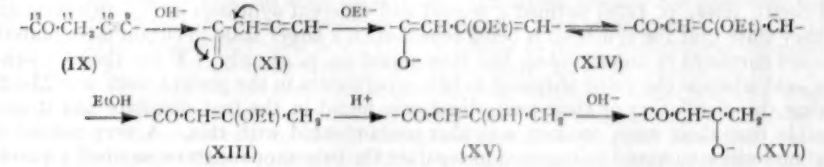


atoms in functional groupings—hydroxyl, oxo, and carboxylic acid—and the structure was readily demonstrated by Schmidt degradation to sebacic acid. The compound must therefore be (±)-12-hydroxy-10-oxo-octadecanoic acid (XII) formed by the reduction of the 12-oxo-grouping of 12-oxo-octadec-9-ynoic acid and the formal hydration of the acetylene linkage. In agreement, its oxidation product showed the typical spectroscopic properties, in alkaline and neutral solution, of a 1 : 3-diketone. The hydration is abnormal on two counts. First, the reaction conditions were such that hydration of a triple bond would not normally be expected and, secondly, the direction of the hydration is abnormal. Thus when (+)-12-hydroxyoctadec-9-ynoic acid is treated with sulphuric acid and a mercury catalyst (Goldsobel, *loc. cit.*; Mangold, *Monatsh.*, 1894, **15**, 307) it is (+)-12-hydroxy-9-oxo-octadecanoic acid (X) which is produced. This has been firmly established by Beckmann degradation of its ketoxime and isolation of azelaic acid. The preparation of (±)-12-hydroxy-9-oxo-octadecanoic acid by such a method is described in the Experimental section. The melting points of the (±)-12-hydroxy-9- and -10-oxo-acids are markedly depressed on admixture.

The reason for the abnormal hydration was made clearer by the observation that 12-oxo-octadec-9-ynoic acid is remarkably unstable to alkali. Thus, although this compound showed no significant high-intensity ultraviolet absorption in neutral or acidic medium, when dissolved in 0·64% sodium hydrogen carbonate solution it had maximal absorption, after one hour, at 226 mμ (ε 11,450). Alcoholic potassium hydroxide (N/1000) gave a solution with maximum absorption at 223 mμ (ε 11,550) three minutes after dissolution of the keto-acetylene. This absorption then began to decline and a new maximum eventually appeared at 263 mμ. Absorption at 223—226 mμ is consistent with the presence of an α-unsaturated ketone grouping and strongly suggests that an allenic αβ-diunsaturated ketone is responsible since the β-double bond, being at right angles to the α-bond, is chromophorically ineffective (Celmer and Solomons, *J. Amer. Chem. Soc.*, 1953, **75**, 1372; Jones, Shaw, and Whiting, *J.*, 1954, 3212). The presence of this chromophore was fully established by isolation of the crude allene, m. p. 28—31° : it showed the infrared absorption characteristic of the CO·CH=C=CH grouping. When its sodium salt was treated with potassium borohydride in methanol, working up under mild conditions without the addition of alkali gave a hydroxy-acid whose infrared spectrum indicated removal of the allene grouping. The initiating step in the abnormal hydration is thus allene formation and this is followed by attack at $C_{(10)}$. Very recently, a similar ready isomerisation of a β-acetylenic acid (but-3-ynoic acid) to an α-allenic acid has been reported as proceeding under mild alkaline

conditions (Eglinton, Jones, Mansfield, and Whiting, *J.*, 1954, 3197). Dr. M. C. Whiting has also informed us that the reaction R·C≡C·CHMe·CHO ⟶ R·CH:C:CMe·CHO can be effected by shaking with sodium hydrogen carbonate solution.

It was mentioned above that in ethanolic 0·001N-alkali, a new absorption at 263 mμ gradually replaces that due to conjugated oxo-allene. In ethanolic 0·01N-potassium hydroxide, maximum intensity (see Table) is reached in 30 min. and the absorption is ascribed to the enol ether (XIII). Formation of the latter may be represented as attack of OEt^- at $C_{(10)}$ to give the resonating anion (XIV) which acquires a proton at $C_{(9)}$ by reaction with the solvent. When the solution is acidified (to 0·12N with hydrochloric acid), there is no sudden change in light absorption: this suggests that the absorption in alkaline solution was due to (XIII) rather than (XIV). However, there is a small drop in intensity and maximal absorption moves to longer wavelength, becoming stationary after 1 hr. This is interpreted as being due to acidic cleavage of the enol ether to the 1 : 3-diketone (XV) since, if the solution is now made alkaline, the maximum shifts to a position characteristic of the enolate ion (XVI), intensity being greatly increased. The crude product from these reactions was isolated and had a strong infrared band at 1579 cm.$^{-1}$ as expected for a 1 : 3-diketone (Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 1954, p. 114, gives 1540—1640 cm.$^{-1}$). The sequence of changes may be summarised:



this suggests that the product from the reaction of the allene (XI) with potassium borohydride in methanol is an enol ether, the 12-oxo-function then being reduced in the usual way. Such enol ethers are known to be readily hydrolysed by acid and the 10-oxo-grouping probably appears during working up with mineral acid.

	$\lambda_{max.}$	ε
Me·$[CH_2]_5$·CO·CH:C(OEt)·$[CH_2]_8$·CO_2H (XIII) [1]	263	11,900
Me·$[CH_2]_5$·CO·CH:C(OH)·$[CH_2]_8$·CO_2H (XV) [1]	275	11,300 [a,c]
Me·$[CH_2]_5$·CO·CH:C(·O⁻)·$[CH_2]_8$·CO_2H (XVI) [1]	297	24,000
Me·C(OMe):CH·COMe [2,4]	257	13,600
Me·C(·O⁻):CH·COMe [2,5]	293	21,800
Me·$[CH_2]_7$·CO·CH:C(OH)·$[CH_2]_7$·CO_2H [2,6]	275	10,500 [a,b]
	276	15,900 [a,c]
Me·$[CH_2]_7$·CO·CH:C(·O⁻)·$[CH_2]_7$·CO_2H [2,7]	296	22,800

For conciseness, tautomeric forms and resonance possibilities are not illustrated.

[1] For conditions of measurement see text. [2] Eistert, Merkel, and Reiss, *Chem. Ber.*, 1954, **87**, 1513. [3] Nunn, *J.*, 1952, 313. [4] In hexane. [5] In 5N-sodium hydroxide. [6] In ethanol. [7] In ethanolic sodium hydroxide. [8] The ε for 1 : 3-diketones is concentration-dependent because of their tautomeric character: (*a*) *c*, 0·00013, (*b*) *c*, 0·0001, (*c*) *c*, 0·000014 mole/l.

The total synthesis of (±)-ricinoleic acid was completed by semihydrogenation of (±)-12-hydroxyoctadec-9-ynoic acid (which was now available in quantity *via* the degradation procedure) with a palladium catalyst poisoned by lead and quinoline (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446). Trial experiments, differing from the above only in that the quinoline was omitted, had shown that this reduction proceeded selectively and stereospecifically in the (+)-series to give partially synthetic (+)-ricinoleic acid, but the semihydrogenation procedure was much less satisfactory in the case of 12-oxo-octadec-9-ynoic acid because of unselectivity. The totally synthetic (±)-ricinoleic acid was purified by low-temperature crystallisation and had m. p. 23—24°. It was characterised as its *p*-bromophenacyl ester. The infrared spectrum of its methyl ester (liquid film) was indistinguishable from that of natural methyl (+)-ricinoleate.

Ricinstearolic acid is closely related in structure to ximenynic acid (octadec-*trans*-11-en-9-ynoic acid) which occurs in the seed fats of three species of the genus *Ximenia* (family

Olacaceae) (Ligthelm and Schwartz, *J. Amer. Chem. Soc.*, 1950, **72**, 1868; Ligthelm, Schwartz, and von Holdt, *J.*, 1952, 1088), and two of the *Santalum* genus (family Santalaceae) (Hatt and Szumer, *Chem. and Ind.*, 1954, 962). Hatt and Szumer also consider that santalbic acid (from the seeds of *Santalum album* Linn., the sandalwood tree; see Madhuranath and Munjanath, *J. Indian Chem. Soc.*, 1938, **15**, 389) is identical with ximenynic acid and this has been confirmed by Gunstone and McGee (*Chem. and Ind.*, 1954, 1112). As methyl ximenynate should be obtainable from methyl ricinstearolate merely by direct dehydration, the latter was treated with phosphorus oxychloride in pyridine but the product was a mixture of enyne and methyl 12-chloro-octadec-9-ynoate. Dehydrohalogenation was completed by heating under reflux with quinoline, and the product had the correct analysis for methyl ximenynate though its ultraviolet absorption indicated that it was as yet only 76% pure. Experiments aimed at its purification were discontinued when Grigor, MacInnes, and McLean (*Chem. and Ind.*, 1954, 1112) reported that methyl ricinstearolate had been converted into its chloro-compound and dehydrohalogenated with methanolic potassium hydroxide to octadec-*trans*-11-en-9-ynoic acid which was identical with ximenynic acid. Our synthesis of (±)-ricinstearolic acid therefore embraces a total synthesis of ximenynic acid [with the reservation that (+)-acid is used for the interconversion step].

Soon after the appearance of our preliminary communication (*loc. cit.*), Kendall, Lumb, and Smith (*ibid.*, p. 1228) notified a second and different synthesis of (±)-ricinoleic acid. As they state that the synthesis is being repeated on a larger scale to obtain more material, detailed comment is unwarranted, but they report m. p. of only +3° for their (±)-ricinoleic acid whereas the value obtained in two experiments in the present work was 23—24°. During the distillation of their acid, diene was found in the first distillate and it seems possible that their main product was also contaminated with this. A very refined distillation technique would be required to separate the two components on so small a quantity (240 mg.). Nevertheless the spectrum of their acid in the infrared was closely similar to that of (+)-ricinoleic acid, though their implied criteria of identity, involving melting points of active and inactive forms, require reconsideration.

Experimental

Analyses were carried out in the Microanalytical Laboratory (Mr. F. H. Oliver) of this Department. The ultraviolet light absorptions were measured in pure ethanol with a Unicam instrument.

Dec-1-yn-4-ol (II).—Propargyl bromide, b. p. 32°/75 mm., n_D^{22} 1·4937, was prepared by Kirrmann's method (*Bull. Soc. chim. France*, 1926, **39**, 698) in 77—80% yields.

(a) *Grignard method.* Magnesium (4·0 g.) was covered with ether (dried over sodium), and propargyl bromide (20·0 g.) in ether (20 ml.) was added dropwise. Mercuric chloride (50 mg.) was used to initiate the vigorous reaction. When addition was complete the product was heated under reflux for 10 min., then cooled, and heptaldehyde (21·0 g.) in ether (20 ml.) added at such a rate that the ether refluxed gently. The product was heated under reflux for 1 hr., set aside overnight, and finally poured into ice and dilute sulphuric acid. The ether layer was separated, dried (K_2CO_3), and distilled to give *dec-1-yn-4-ol* (6·0 g., 23%), b. p. 57°/0·06 mm., n_D^{22} 1·4490 (Found: C, 77·6; H, 11·85. $C_{10}H_{18}O$ requires C, 77·85; H, 11·75%). In a second experiment the yield was 4·4 g. (17%).

(b) *Reformatski method.* Zinc wool (37 g.), etched with dilute hydrochloric acid, was washed with water, methanol, and dry ether. Tetrahydrofuran (50 ml.; dried over sodium) was added, together with mercuric chloride (50 mg.). Heptaldehyde (61 g.) and propargyl bromide (51 g.) were mixed with tetrahydrofuran (100 ml.) and added to the zinc with shaking, at such a rate that gentle refluxing was maintained. Finally the mixture was heated under reflux for 30 min. and poured into ice-cold dilute acetic acid. The upper layer was united with two ethereal extracts of the aqueous phase (previously saturated with salt). Drying (Na_2SO_4), evaporation, and distillation yielded dec-1-yn-4-ol (55·4% in the best experiment). In other cases the yield was 46—50%. Absorption at 1953 cm.$^{-1}$ (C:C:C), as well as at 2146 and 3262 cm.$^{-1}$ (·C:CH), showed that the allene (III) was also present.

(±)-4-(*Tetrahydro-2-pyranyloxy*)*dec*-1-*yne*.—Dec-1-yn-4-ol (56 g.) was mixed with dihydropyran (32 g.). On the addition of two drops of concentrated hydrochloric acid, the mixture became warm, and after ice-cooling was set aside overnight. Solid potassium hydroxide was added and the liquid decanted. A few cg. of potassium carbonate were added and on distillation 4-(*tetrahydro-2-pyranyloxy*)*dec*-1-*yne* (73 g., 84%), b. p. 84°/10^{-3} mm., n_D^{22} 1·4588, was isolated (Found: C, 75·25; H, 11·05. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%).

1-*Chloro*-6-*iodohexane*.—This was prepared according to the directions of Raphael and Sondheimer (*J.*, 1950, 2100). 1 : 6-Hexanediol was first converted into 1 : 6-dichlorohexane, b. p. 92—93°/13 mm., n_D^{23} 1·4595, in 88·5% yield. Dichlorohexane (245 g.) in acetone (1·5 l.) when treated with sodium iodide (245 g.) gave a fraction, b. p. 45—59°/0·5 mm., n_D^{21} 1·4719 (88 g., mainly recovered dichlorohexane), and one of b. p. 66—69°/0·5 mm., n_D^{21} 1·5234—1·5245 (145 g., the required iodochloride).

(±)-1-*Chloro*-10-(*tetrahydro-2-pyranyloxy*)*hexadec*-7-*yne* (V).—Sodamide was prepared in liquid ammonia (500 ml.) from sodium (2·0 g.), 4-(tetrahydro-2-pyranyloxy)dec-1-yne (9·0 g.) added, and the solution stirred for 90 min. 1-Chloro-6-iodohexane (9·0 g.) was then added dropwise and the solution stirred overnight. The ammonia was allowed to evaporate and water (100 ml.) added cautiously. The residue, after extraction with ether, drying, and evaporation, was distilled, to yield 1-*chloro*-10-(*tetrahydro-2-pyranyloxy*)*hexadec*-7-*yne* (5·6 g., 42%), b. p. 164°/10^{-6} mm., n_D^{23} 1·4772 (Found: Cl, 10·05. $C_{21}H_{37}O_2Cl$ requires Cl, 9·95%). The fractions which boiled at higher temperatures than the starting materials but below the above product gave higher chlorine analyses than expected for the above formula and probably represent material from which the tetrahydropyranyl grouping has been eliminated.

(±)-12-*Hydroxyoctadec*-9-*ynoic acid* (VII).—1-Chloro-10-(tetrahydro-2-pyranyloxy)hexadec-7-yne (3·99 g.) was heated under reflux with sodium iodide (3·5 g.) in acetone (50 ml.) for 7 hr.; sodium chloride was precipitated. After pouring into water and extraction with ether, the extracts were dried and evaporated to yield crude 1-iodo-10-(tetrahydro-2-pyranyloxy)hexadec-7-yne. This was added to a solution of diethyl sodiomalonate prepared from diethyl malonate (1·96 g.), sodium (0·28 g.), and ethanol (20 ml.), and the mixture heated under reflux for 17 hr., then cooled. Potassium hydroxide (4·0 g.) in methanol (40 ml.) and water (2 ml.) was added and hydrolysis allowed to proceed at 25° for 44 hr. The product was poured into water and extracted with ether to eliminate non-acidic materials (0·8 g.). Acidification (sulphuric acid) of the aqueous phase, followed by ether-extraction, produced the oily malonic acid (2·22 g.). This was heated at 10^{-6} mm. with a jacket-temperature of 140° for 2 hr. during which the majority distilled. This distillate was then heated under reflux for 30 min. with 2N-sulphuric acid and extracted with ether. Extraction of the latter phase with dilute aqueous sodium hydroxide, followed by acidification and isolation with ether in the usual way, yielded (±)-12-*hydroxyoctadec*-9-*ynoic acid* [(±)-ricinstearolic acid], m. p. 51—52°. This was twice crystallised from light petroleum (b. p. 80—100°) to yield the pure acid (255 mg., 7·7%), m. p. 53·0—53·5° (Found: C, 72·5; H, 10·8. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%). The *p-bromophenacyl ester* crystallised from ethanol in plates, m. p. 82° (Found: C, 62·85; H, 7·65. $C_{26}H_{37}O_4Br$ requires C, 63·25; H, 7·55%). The m. p.s of the acid and its derivative were not depressed when appropriately mixed with (±)-ricinstearolic acid and its *p*-bromophenacyl ester prepared from natural (+)-ricinoleic acid.

(+)-12-*Hydroxyoctadec*-9-*ynoic Acid* [(+)-*Ricinstearolic Acid*].—Methyl (+)-ricinoleate was isolated from castor oil by the procedure given in "Biochemical Preparations," Vol. II, and distilled at low pressure through a 12" vacuum-jacketed column, packed with glass helices. Attempts to distil at 0·2 mm. through a high-efficiency electrically heated column with Stedman gauze packing caused considerable decomposition and formation of water and heptaldehyde. Castor oil (B.P.) (235 g.) yielded methyl ricinoleate (133·5 g.), b. p. 181—182°/0·15 mm., n_D^{22} 1·4620, m. p. −6°, $[\alpha]_D^{22}$ 5·10° (homogeneous). Recorded data (*op. cit.*; Brown and Green, *J. Amer. Chem. Soc.*, 1940, **62**, 738; Walden, *Ber.*, 1903, **36**, 782): b. p. 185—187°/2·0 mm., n_D^{20} 1·4629, m. p. −4°, $[\alpha]_D^{22}$ 5·05°.

Methyl ricinoleate (135 g.) was suspended in water (450 ml.), and bromine (90 g.) added with continuous shaking. A heavy oil separated. This was taken up in ether, separated, and washed with water and dilute sodium carbonate solution. After drying and evaporation, the residual crude dibromide was heated under reflux with excess of 10% ethanolic potassium hydroxide for 20 hr. Water was added and the acidified solution extracted with ether. The extracts were dried and evaporated; a thick oil remained which solidified on cooling. After several crystallisations from light petroleum (b. p. 60—80°) it melted at 52°. The yield of (+)-ricinstearolic acid was 50·5 g. (39%), $[\alpha]_D^{22}$ 13·2° (*c* 53% in acetone). Iyer, Sudborough,

and Ayyer (*J. Indian Inst. Sci.*, 1925, **8**, *A*, 29) give $[\alpha]_D$ 13·67° (in acetone). The p-*bromophenacyl ester* crystallised from ethanol in plates, m. p. 63° (Found : C, 63·2; H, 7·7; Br, 16·45. $C_{36}H_{57}O_4Br$ requires C, 63·3; H, 7·55; Br, 16·2%). The 3 : 5-dinitrobenzoate and α-naphthylurethane were obtained as oils; the *S*-benzylthiuronium salt melted at 125° but its tendency to give unsharp values, dependent on the rate of heating (cf. Berger, *Acta Chem. Scand.*, 1954, **8**, 427), renders it an unsuitable derivative. When (+)-ricinstearolic acid was admixed with the (±)-acid, its m. p. was depressed to 49°. The preparative method used above is based on the directions of Grün and Woldenburg (*loc. cit.*).

12-*Oxo-octadec-9-ynoic acid* (IX).—To (+)-ricinstearolic acid (28·5 g.) in acetone (360 ml.) chromic acid (6·6 g.) in concentrated sulphuric acid (10·6 g.) and water (made up to 33 ml.) was added slowly at 0° (thermometer in liquid), with vigorous stirring. The mixture was stirred at 0° for a further hour, water (1 l.) added, and the solution extracted three times with ether. After drying (Na_2SO_4), the extracts were evaporated *in vacuo* and the pale yellow solid which remained crystallised from ethanol, to give 12-*oxo-octadec-9-ynoic acid* as waxy plates, m. p. 62—64° (15·5 g., 55%). Further crystallisation raised the m. p. to 64—64·5° (Found : C, 73·3; H, 10·45. $C_{18}H_{30}O_3$ requires C, 73·4; H, 10·25%). The substance deteriorates slowly.

Complete hydrogenation in the presence of 3% palladium–calcium carbonate gave 12-*oxostearic acid*, m. p. 82° after crystallisation from methanol (Found : C, 72·25; H, 11·45. $C_{18}H_{34}O_3$ requires C, 72·45; H, 11·5%). As the m. p. differences among the oxostearic acids are small, 12-oxostearic acid was prepared by oxidation of (+)-12-hydroxystearic acid (0·78 g.) with chromic acid (0·19 g.) in glacial acetic acid (10 ml.) at 100° for 10 min. Under these conditions the oxidation was not complete, so the product was oxidised further with chromic acid (0·093 g.) in glacial acetic acid (10 ml.) for 10 min. The product was poured into water, and the solid removed and recrystallised from methanol as white plates, m. p. 82° (0·60 g.) (Bergström, Aulin-Erdtman, Rolander, Stenhagen, and Östling, *Acta Chem. Scand.*, 1952, **6**, 1157, give m. p. 81·5—81·9°). On admixture with the above specimen there was no depression of m. p.

Partial Hydrogenation of 12-*Oxo-octadec-9-ynoic Acid*.—The acid (0·26 g.) was dissolved in methanol (5 ml.) and hydrogenated in the presence of Lindlar catalyst (*loc. cit.*; 100 mg.). When hydrogen (21 ml. at 19°/760 mm.) had been absorbed (calc. for semihydrogenation, 21 ml.), the reaction was discontinued and the catalyst removed. Evaporation, and crystallisation from methanol, yielded white crystals (100 mg.), m. p. 72—75°, which after three further crystallisations gave 12-oxostearic acid, m. p. 81—82° undepressed with the specimen prepared as above. This demonstrates that the hydrogenation was not fully selective. From the mother-liquors a small amount of solid, m. p. 34—35°, was isolated. A second hydrogenation with the oxoacetylenic acid (0·82 g.), ethyl acetate (10 ml.), and Lindlar catalyst (0·40 g.) was carried out, absorption of 68 ml. of hydrogen (19°/760 mm.) being permitted (Calc. for semihydrogenation 66·8 ml.). The product was worked up and higher-melting material eliminated by crystallisation, attention being concentrated on the mother-liquors. Crystallisation of the product from these from 80% ethanol and then light petroleum (b. p. 40—60°) gave a material, m. p. 38—39·5°, which was unstable and is probably the expected 12-oxo-oleic acid. This was described by Ellis (*J.*, 1950, 9), who records its m. p. as 39°.

(±)-12-*Hydroxyoctadec-9-ynoic acid* (VII).—To 12-oxo-octadec-9-ynoic acid (3·13 g.) in methanol (140 ml.) a solution of potassium borohydride (0·95 g., 7 equivs.) in water (10 ml.) was added. The mixture was set aside for 16 hr. at 0°, 10% aqueous sodium hydroxide (60 ml.) added, and the solution heated at 45° for 15 min. Water and dilute hydrochloric acid were added. Ether-extraction, drying, and evaporation gave a white solid, m. p. 50—51°. Recrystallisation from acetone at low temperature yielded (±)-12-*hydroxyoctadec-9-ynoic acid* (2·65 g., 85%), m. p. 53—53·5° (Found : C, 72·7; H, 10·85; microhydrogenation, $1·8H_2$. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%). Its *p*-bromophenacyl ester had m. p. 82° Meerwein–Pondorff reduction of the methyl ester of (IX) gave only oils.

(±)-12-*Hydroxy*-10-*oxo-octadecanoic acid* (XII).—12-Oxo-octadec-9-ynoic acid (0·42 g.) was neutralised in methanol (10 ml.) with a solution of sodium methoxide in methanol. Potassium borohydride (47·4 mg., 2 equivs.) was added in water (1·0 ml.), and the solution heated at 50° for 1 hr. 2N-Sodium hydroxide was then added and heating continued for 15 min. The mixture was made well acid with dilute mineral acid to give (±)-12-*hydroxy*-10-*oxo-octadecanoic acid* (178 mg., 40%), m. p. 77—79°, raised by recrystallisation from acetone to 82—82·5° (Found : C, 68·85; H, 11·1; microhydrogenation $0·65H_2$. $C_{18}H_{34}O_4$ requires C, 68·75; H, 10·9%; microhydrogenation, $1·0H_2$ for complete reduction of an oxo grouping, which proceeds slowly with Adams catalyst in glacial acetic acid, under the conditions employed). The infrared

spectrum showed the presence of hydroxylic (3195 and 3290 cm.$^{-1}$), carbonyl (1687 cm.$^{-1}$), and carboxylic (1702 cm.$^{-1}$) absorption. The *p-bromophenacyl ester*, crystallised from ethanol, had m. p. 90—90·5° (Found: C, 60·95; H, 7·75. $C_{26}H_{39}O_5Br$ requires C, 61·05; H, 7·7%). A *semicarbazone* was obtained as plates, m. p. 108·5—109·5°, from ethanol (Found: C, 61·1; H, 9·9; N, 11·15. $C_{19}H_{37}O_4N_3$ requires C, 61·4; H, 10·05; N, 11·3%). The α-naphthylurethane formed plates, m. p. 48°, from light petroleum (b. p. 100—120°).

The keto-alcohol (XII) (77 mg.) was dissolved in acetone (2·0 ml.), and chromic acid (17·2 mg., in 0·5 ml. of water containing a drop of sulphuric acid) was added. After 3 hr. the solution was extracted with ether and worked up in the usual way. Light-absorption data for the crude product, which had only partially oxidised, were $\lambda_{max.}$ 275 mμ (ε 1480 in neutral ethanol), changed to $\lambda_{max.}$ 298 mμ (ε 3530) on the addition of alkali. The absorption, which is characteristic of a 1 : 3-dioxo-compound, is due to 10 : 12-dioxo-octadecanoic acid. Nunn (*J.*, 1952, 313) records that 9 : 11-dioxononadecanoic acid has maximal absorption at 275 mμ: in alkaline solution this shifts to 296 mμ and the ε of the compound, which is concentration-dependent, is increased 2·17-fold.

A series of experiments was carried out on the conditions of the borohydride reduction. If the acid was neutralised before reduction, with sodium hydroxide or sodium methoxide, either (±)-12-hydroxy-10-oxo-octadecanoic acid or intractable oils were obtained, although very occasionally small amounts of (±)-12-hydroxyoctadec-9-ynoic acid were formed. Water or methanol containing considerable amounts of water tended to give oils when used as the solvent. Only when the borohydride was added to the free acid was (±)-12-hydroxyoctadec-9-ynoic acid obtained in good yield.

(±)-12-*Hydroxy*-9-*oxo-octadecanoic acid* (X).—(±)-12-Hydroxyoctadec-9-ynoic acid (130 mg.) was hydrated with sulphuric acid and a mercury catalyst in the usual way, to give (±)-12-*hydroxy*-9-*oxo-octadecanoic acid* (24 mg.), m. p. 83·5° (Found: C, 68·5; H, 11·0. $C_{18}H_{34}O_4$ requires C, 68·75; H, 10·9%). On admixture of this with the 10-keto-isomer of m. p. 82°, the m. p. was 70—76°.

Schmidt Degradation of (±)-12-*Hydroxy*-10-*oxo-octadecanoic Acid*.—The hydroxy-keto-acid (310 mg.) was added to chloroform (1·6 ml.) and concentrated sulphuric acid (0·8 ml.), and then cooled in ice. Sodium azide (65·2 mg.) was added in small portions to the stirred solution. After 15 min. the solution was poured into ice-water and extracted with chloroform. The extracts were dried and evaporated and the partly solid product was heated for 3½ hr. in a sealed tube at 100° with concentrated hydrochloric acid (1·5 ml.). The solution was made alkaline, neutral material removed with ether, and the acid liberated and collected in the usual way. The oily acid was dissolved in hot water and filtered through kieselguhr to remove oil, and the filtrate was cooled. A colourless acid, m. p. 127°, crystallised. This m. p. was raised to 131° (20 mg.) by another crystallisation. The m. p. was undepressed by admixture with sebacic acid, m. p. 133°.

Action of Alkali on 12-*Oxo-octadec*-9-*ynoic Acid* (IX).—The acid (269 mg.) was dissolved in ethanol (25 ml.) containing N-potassium hydroxide (1 ml.; 0·92 ml. is required for neutralisation of the acid). The ultraviolet light absorption, three minutes after dissolution, was $\lambda_{max.}$ 223 mμ (ε 14,200). The mixture was at once added to a solution containing N-hydrochloric acid (1·1 ml.) and extracted with ether. Evaporation of the dried extract yielded a pale yellow oil which at 0° set to a solid, m. p. 28—31° (XI). It was not further purified. The infrared spectrum (paraffin mull) showed strong absorption at 1952 (allene), 1706 (carboxyl), and 1678 cm.$^{-1}$ (α-unsaturated ketone). There was no significant absorption in the olefinic CH out-of-plane deformation region (950—1010 cm.$^{-1}$).

Action of Potassium Borohydride on the Oxo-allene (XI).—Crude allene (m. p. 28—31°; 93 mg.) was dissolved in methanol (4 ml.), cooled in ice-salt, and neutralised to phenolphthalein with 0·2N-sodium hydroxide. Potassium borohydride (14·8 mg.) was added and the solution set aside at 0° for 12 hr. It was poured into dilute acid, and the oily product isolated with ether. This showed absorption at 3390 cm.$^{-1}$ (hydroxyl) (liquid film) but there was no absorption in the allenic or acetylenic region, or between 950 and 1010 cm.$^{-1}$.

Dehydration of Methyl Ricinstearolate.—Ricinstearolic acid (5·0 g.) in ether was titrated with ethereal diazomethane to a permanent yellow colour. The solvent was evaporated under reduced pressure, leaving crude methyl ricinstearolate which was dissolved in dry pyridine (10 ml.) and treated slowly with phosphorus oxychloride (5·0 g.) in pyridine (10 ml.). The reactants were stirred for 2 hr. and then heated on a steam-bath for 30 min. Dilute sulphuric acid was added at 0° and the solution extracted with ether. The extracts were washed, dried, evaporated, and distilled, to give *methyl* 12-*chlororicinstearolate* (2·7 g., 54%), b. p. 148—149°/10^{-3} mm.,

n_D^{20} 1·4682 (Found: C, 70·9; H, 10·3; Cl, 8·95; microhydrogenation 2·1H_2. $C_{19}H_{33}O_2Cl$ requires C, 69·4; H, 10·1; Cl, 10·8%). The analytical results and the ultraviolet light absorption ($\lambda_{max.}$ 227 mμ; ε 1950) demonstrate contamination with methyl ximenynate. Ligthelm, Schwartz, and von Holdt (*loc. cit.*) give $\lambda_{max.}$ 229 mμ (ε 16,030) for pure methyl ximenynate.

The above 12-chlororicinstearolic ester (5·4 g.) was heated under reflux with quinoline (9·6 g.) for 1 hr. in a nitrogen atmosphere. The cooled solution was poured into dilute sulphuric acid at 0°, extracted, and worked up in the usual manner. The product had b. p. 143—144°/0·05 mm., n_D^{21} 1·4717, $\lambda_{max.}$ 226 mμ (ε 10,510) (Found: C, 77·85; H, 11·0. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·05%). Ligthelm *et al.* give n_D^{25} 1·4700. In a second experiment the light absorption was $\lambda_{max.}$ 228 mμ (ε 12,260), *i.e.*, the substance was approx. 76% pure.

Methyl (+)-*Ricinoleate* (*Partially Synthetic*).—(+)-12-Hydroxyoctadec-9-ynoic acid (1·00 g.; derived from the degradation of natural material, see above) was hydrogenated in methanol (12 ml.) with Lindlar catalyst (1·0 g.), absorption being interrupted just before uptake of 1 mol. of hydrogen. The catalyst was removed, the methanol evaporated, and the oil treated with diazomethane in ether and distilled. Methyl (+)-ricinoleate (0·89 g.), b. p. 167°/0·15 mm., n_D^{20} 1·4629, $[\alpha]_D^{22}$ 5·0° ±0·2° (*c* 10% in EtOH) was obtained. After hydrolysis a p-*bromophenacyl ester* was prepared which crystallised from ethanol in plates, m. p. 58° (Found: C, 62·85; H, 8·15. $C_{26}H_{39}O_4Br$ requires C, 63·0; H, 7·95%). The hydroxamic acid was prepared by adding methyl (+)-ricinoleate (3·14 g.) in ethanol (30 ml.) to hydroxylamine hydrochloride (0·84 g.) in methanol (6 ml.). The solution was treated slowly with sodium (0·50 g.) in ethanol (20 ml.), and the resulting solution set aside at 20° for 3 days. Sodium chloride was removed by filtration and the product neutralised with ice-cold dilute hydrochloric acid. Water was added and the product filtered off and recrystallised from ethyl acetate as waxy plates, m. p. 63° (1·85 g.) (Found: C, 69·25; H, 11·3. $C_{18}H_{35}O_3N$ requires C, 69·0; H, 11.25%). Yukawa and Inoue (*J. Agric. Chem. Soc. Japan*, 1942, **18**, 875; *Bull. Agric. Chem. Soc. Japan*, 1942, **18**, 72; cf. *Chem. Abs.*, 1951, **45**, 8449) give m. p. 65·5°.

(±)-*Ricinoleic Acid*.—(±)-12-Hydroxyoctadec-9-ynoic acid (1·06 g.) in methanol (10 ml.) containing Lindlar catalyst (0·5 g.) and quinoline (5 drops) was hydrogenated. When hydrogen (83·2 ml.) had been absorbed at 29°/766 mm. (required for semihydrogenation 83·1 ml.), the reaction was interrupted and the catalyst filtered off. Dilute hydrochloric acid was added to the filtrate and the mixture extracted with ether. The extract was washed with dilute hydrochloric acid, then water, and dried and evaporated. The residual oil was crystallised from acetone at −70° to give totally synthetic (±)-*ricinoleic acid* (0·80 g.), m. p. 23—24°, n_D^{19} 1·4723 (supercooled) (Found: C, 72·15; H, 11·6. $C_{18}H_{34}O_3$ requires C, 72·45; H, 11·5%). Hawke (*J. S. African Chem. Inst.*, 1949, **2**, 125) gives n_D^{25} 1·4703 for pure natural (+)-ricinoleic acid. The p-*bromophenacyl ester* had m. p. 62—63° and crystallised from ethanol in plates (Found: C, 62·95; H, 8·0. $C_{26}H_{39}O_4Br$ requires C, 63·0; H, 7·95%). (±)-Ricinoleic acid (410 mg.) with diazomethane gave the *methyl ester* (260 mg.), b. p. 178°/1 mm., n_D^{16} 1·4638 (Found: C, 73·1; H, 11·75; microhydrogenation, 0·95H_2. $C_{19}H_{36}O_3$ requires C, 73·05; H, 11·6%). Its infrared spectrum (liquid film) was not distinguishable from that of natural methyl (+)-ricinoleate.

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Chemistry Department, Imperial College of Science and Technology,
S. Kensington, London, S.W.7. [*Received, December 30th*, 1954.]

*The Reactions of Highly Fluorinated Organic Compounds. Part IX.** 1H-*Decafluoro-4-trifluoromethylcyclohexane, Nonafluoro-4-trifluoromethylcyclohex-1-ene, and Perfluoro-(3-methyladipic) Acid.*

By G. B. Barlow, M. Stacey, and J. C. Tatlow.

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Perfluoro-(1-methyl-4-*iso*propyl*cyclo*hexane) with bromine, chlorine, or toluene at 500—550° gave, respectively, 1-bromo- 1-chloro- and decafluoro-*cyclo*hexane or 1*H*-decafluoro-4-trifluoromethyl*cyclo*hexane. The chlorofluorocarbon was made also by vapour-phase fluorination of *p*-chlorotoluene or *p*-chlorobenzotrifluoride with cobaltic fluoride, and with lithium aluminium hydride it afforded the fluorohydrocarbon. The latter, with concentrated aqueous alkali, was dehydrofluorinated to nonafluoro-4-trifluoromethyl-*cyclo*hex-1-ene, oxidation of which gave perfluoro-(3-methyladipic) acid; from this, by decarboxylation, 1*H* : 4*H*-heptafluoro-2-trifluoromethylbutane was made. Some preliminary observations on the stability of fluorohydrocarbons to alkali are recorded.

This paper describes further applications of processes developed in this Department for the synthesis of highly fluorinated compounds and described in earlier papers in this series. We have shown that the carbon–carbon bonds between two tertiary carbon atoms in certain fluorocarbons can be broken preferentially in pyrolysis-type reactions (Barlow and Tatlow, *J.*, 1952, 4695). In an analogous manner, perfluoro-(1-methyl-4-*iso*propyl*cyclo*hexane), made by reaction of *p*-cymene with cobaltic fluoride, reacted with bromine, chlorine, or toluene when a mixture of the two was passed through a hot tube at temperatures of about 510°, 550°, and 550° respectively (owing to a calibration error, the temperatures quoted in the earlier paper are all too high by 100°; the actual temperatures used were similar to those given above). With bromine, 1-bromodecafluoro-4-trifluoromethyl*cyclo*hexane and a low-boiling product, probably 2-bromoheptafluoropropane, were formed; with chlorine the analogous chloro-derivatives were obtained. From the reaction with toluene, 1*H*-decafluoro-4-trifluoromethyl*cyclo*hexane, 2*H*-heptafluoropropane (probably), and dibenzyl were the principal products. The fluorocarbons, perfluoro-(di*cyclo*hexyl), -(*iso*propyl-*cyclo*hexane), and -(1-methyl-4-*iso*propyl*cyclo*hexane) were pyrolysed alone, or in the presence of perfluoro(methyl*cyclo*hexane) or nitrogen, at temperatures similar to those at which reaction with chlorine, bromine, or toluene occurs. In all cases, profound decomposition resulted but no recognisable products were isolated. Under these conditions, with no "reactive" carrier gas present the intermediates seemed to be capable of effecting extensive rupture of carbon–carbon bonds in themselves or in undissociated fluorocarbons present.

These reactions again illustrate that, in some fluorocarbons, bonds between tertiary carbon atoms may be cleaved more readily than bonds involving primary and secondary carbon atoms. In this particular case, though the *cyclo*hexane ring carried a second side chain, reaction occurred less readily at that point. It was suggested earlier (Part II, *loc. cit.*) that these processes are initiated by homolysis of the C–C bonds between tertiary carbon atoms (where both are not in the same ring). It appears that the bond dissociation energies for such linkages between tertiary carbon atoms, in general, are lower than for those involving primary or secondary carbon atoms. It seems likely in fact that the secondary fluorocarbon radicals formed are relatively more stable than primary ones. In accord with this are recent conclusions on the free-radical additions of fluoroalkyl iodides to fluoro-olefins (Haszeldine, *J.*, 1953, 3559, 3565), the direction of addition indicating that, here also, secondary intermediate radicals are more stable than primary.

Alternative methods for the production of 1-chlorodecafluoro-4-trifluoromethyl*cyclo*hexane were the fluorination, in the vapour phase with cobalt trifluoride, of either *p*-chlorotoluene or *p*-chlorobenzotrifluoride. As with other chlorofluorocarbons (Tatlow and

* Part VIII, *J.*, 1955, 1184.

Worthington, *J.*, 1952, 1251; Buxton and Tatlow, *J.*, 1954, 1177; Roylance, Tatlow, and Worthington, *J.*, 1954, 4426), 1-chlorodecafluoro-4-trifluoromethyl*cyclo*hexane reacted with lithium aluminium hydride in diethyl ether, the chlorine atom being replaced by hydrogen. This gave an alternative route to 1*H*-decafluoro-4-trifluoromethyl*cyclo*hexane. Other cyclic polyfluorides (*idem, locc. cit.*; Evans and Tatlow, *J.*, 1954, 3779) undergo dehydrofluorination with concentrated aqueous potassium hydroxide, and, in this case, this type of reaction afforded nonafluoro-4-trifluoromethyl*cyclo*hex-1-ene. The olefin gave dibromo- and dichloro-addition products in the usual way. Oxidation of it with aqueous potassium permanganate afforded the branched-chain dibasic acid, perfluoro-(3-methyladipic) acid, characterised as the free acid, salts, diethyl ester, and diamide. Identical specimens of the acid and its derivatives were obtained from samples of the olefin derived ultimately from three sources, (*a*) the fluorocarbon–toluene reaction, (*b*) from *p*-chlorotoluene, and (*c*) from *p*-chlorobenzotrifluoride. Decarboxylation of the dipotassium salt of the acid, by the method of LaZerte, Hals, Reid, and Smith (*J. Amer. Chem. Soc.*, 1953, **75**, 4525), gave 1*H* : 4*H*-heptafluoro-2-trifluoromethylbutane. This fluorohydrocarbon was much less susceptible to attack by concentrated aqueous alkali than are cyclic polyfluorides, and, even under drastic conditions, only a small proportion of fluorine was removed. However, alcoholic alkali readily attacked the compound, fluoride ion (approx. 2 mol.) being eliminated under mild conditions, though no definite products were isolated, whilst under drastic conditions virtually all could be removed. It appeared that olefin formation was followed by base-catalysed addition of the alcohol across the unsaturated linkages, and subsequent further elimination of hydrogen fluoride.

The similar properties of analogous samples obtained from the three different sources suggested that isomerisation had not occurred to any serious extent in the original fluorinations. Migration of chlorine can occur during the reaction of chlorohydrocarbons with cobaltic fluoride (Roylance, Tatlow, and Worthington, *loc. cit.*) though the effect is probably more pronounced with polychlorides than with monochlorides. The purity of the volatile compounds prepared was checked by gas–liquid partition chromatography (Evans and Tatlow, *J.*, 1955, 1184). Only in one case, that of 1*H*-decafluoro-4-trifluoromethyl*cyclo*hexane, was more than one component detected. This fluorohydrocarbon gave two peaks, both being present though the relative sizes varied, in samples of the compound from all three sources. The effect may well have been due to the presence of two stereoisomeric forms.

Information available so far suggests that, in fluorohydrocarbons, isolated hydrogen atoms on secondary carbon atoms are susceptible to attack by aqueous potassium hydroxide. Several examples of olefin formation from cyclic polyfluorides are now known (see earlier papers in this series), whilst 3*H*-heptafluoroadipic acid (Barbour, MacKenzie, Stacey, and Tatlow, *J. Appl. Chem.*, 1954, **4**, 341) readily loses fluorine with alkali. Further, the 2*H*-heptafluoropropane obtained from perfluoro(methyl*iso*propyl*cyclo*hexane) was degraded by alkaline permanganate to give trifluoroacetic acid; alkali alone effected the elimination of about 1 atom of fluorine as the ion. In contrast, the hydrogen in terminal CHF_2 groups appears to be much more resistant to attack by bases. Thus, with aqueous alkali, 1*H* : 4*H*-heptafluoro-2-trifluoromethylbutane and 1*H* : 4*H*-octafluorobutane lost, respectively, little and no fluorine. Also, 3*H*-tetrafluoropropionic acid did not give trifluoroacrylic acid (Henne and Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 479). Haszeldine's preparation of 1*H*-perfluoroalkanes from perfluoroalkyl iodides (*J.*, 1953, 3761) indicates that CHF_2 groups also resist attack by alcoholic alkali. The slight attack on 1*H* : 4*H*-heptafluoro-2-trifluoromethylbutane by aqueous alkali, and the ready removal of fluorine by alcoholic alkali, suggest that the isolated fluorine at a branch point next to a CHF_2 group may be, relatively, a point of weakness.

Experimental

Fluorinations with Cobaltic Fluoride.—For a description of the apparatus and general reaction conditions used see Barbour, Barlow, and Tatlow (*J. Appl. Chem.*, 1952, **2**, 127).

(a) p-*Cymene*. This hydrocarbon (43·8 g.; input rate 30 c.c./hr.) was passed through a reaction

vessel maintained at 260—280°. After being poured into ice-water, neutralised, separated, dried, and filtered, the product was fractionated through a 1′ column packed with Dixon gauze spirals. After removal of the low-boiling breakdown products, there was obtained perfluoro-(1-methyl-4-*iso*propyl*cyclo*hexane) (66·0 g.), b. p. 144—146°, n_D^{16} 1·3006. Haszeldine and Smith (*J.*, 1950, 3617) gave b. p. 146·5°, n_D^{25} 1·2965.

(b) p-*Chlorotoluene.* This compound (248·4 g. in all; input rate 20 c.c./hr.) was fluorinated in three runs at 290—310°. After being worked up as described above, the products were combined and fractionated to give, as constant-boiling fractions, perfluoro(methyl*cyclo*hexane) (90·0 g.), b. p. 75·5—75·8°, n_D^{17} 1·285, and 4-*chlorotridecafluoro*(*methyl*cyclo*hexane*) (107·1 g.), b. p. 102—103°, n_D^{17} 1·314 (Found: C, 22·9; F, 67·4%; *M*, 373. C_7ClF_{13} requires C, 22·9; F, 67·4%; *M*, 366·5).

(c) p-*Chlorobenzotrifluoride.* This material (359 g. in all; input rate 20 c.c./hr.) was fluorinated in three runs at 290—310°, to give perfluoro(methyl*cyclo*hexane) (155·0 g.), b. p. 75·5—75·8°, and 4-chlorotridecafluoro(methyl*cyclo*hexane) (168·4 g.), b. p. 101·7—103·1°, n_D^{18} 1·314.

Reactions of Perfluoro-(1-*methyl*-4-iso*propyl*cyclo*hexane*).—These reactions were carried out in a packed hard-glass tube as described by Barlow and Tatlow (*loc. cit.*). Temperatures were measured by chromel–alumel and iron–constantan thermocouples connected to a "Cambridge" potentiometer. In general, the tube and packing were attacked slowly by the reactants, and after a number of runs some etching was visible. The toluene used was "sulphur-free" which had been passed through the tube at 650° and then fractionated.

(a) *With toluene.* The fluorocarbon (52·9 g.; input rate 10 c.c./hr.) and toluene (140 c.c.; input rate 50 c.c./hr.) were passed into the reaction tube which was at 540—555°. When the contents of the trap warmed to room temperature, a low-boiling fraction (*ca.* 7 c.c.), b. p. $< -10°$, probably 2*H*-heptafluoropropane, was obtained. The residue was fractionated through a 1′ column, to give 4H-*tridecafluoro*(*methyl*cyclo*hexane*) (7·9 g.), b. p. 85·1—86·3° (Found: C, 25·5; H, 0·5; F, 74·0%; *M*, 331. C_7HF_{13} requires C, 25·3; H, 0·3; F, 74·4%; *M*, 332). After removal of excess of toluene, the still residue afforded, by the usual isolation techniques, dibenzyl (7·2 g.), m. p. and mixed m. p. 52°.

The gaseous product was treated with potassium hydroxide (10 g.), potassium permanganate (20 g.), and water (40 c.c.) in a rocking autoclave for 18 hr. at 120°. The aqueous phase was reduced (sulphur dioxide), neutralised, and evaporated, and the residue extracted with alcohol. Potassium trifluoroacetate (2·8 g.) was obtained, identified after esterification and subsequent ammonolysis as trifluoroacetamide, m. p. and mixed m. p. 73° (Found: C, 21·2; H, 1·6. Calc. for $C_2H_2ONF_3$: C, 21·25; H, 1·8%), for which Swarts (*Bull. Acad. roy. Belg.*, 1922, **8**, 343) gave m. p. 74·8°. When the gaseous compound was shaken at 10—15° for 16 hr. with concentrated aqueous potassium hydroxide, fluoride ion (0·9 mol.) appeared in the aqueous phase.

(b) *With chlorine.* The fluorocarbon (38·2 g.; input rate 20 g./hr.) and chlorine (*ca.* 6 l./hr.) were allowed to react at 540—555°. The product was washed with ice-cold aqueous sodium hydroxide, then water, and was dried. A low-boiling product, b. p. 0°, probably 2-chloroheptafluoropropane, was given off during this process. Fractionation of the liquid residue afforded 4-chlorotridecafluoro(methyl*cyclo*hexane) (11·4 g.), b. p. 100·7—101·7°, n_D^{14} 1·315 (Found: C, 23·2; F, 67·8%; *M*, 364).

(c) *With bromine.* Bromine (25 g.), in a stream of nitrogen (5 l./hr.), and the fluorocarbon (54.9 g.; input rate 18 g./hr.), at 510°, gave two pure compounds, 2-bromoheptafluoropropane (10·1 g.), b. p. 15—16°, and 4-*bromotridecafluoro*(*methyl*cyclo*hexane*) (8·8 g.), b. p. 115·2—116·1° (Found: C, 20·2; F, 59·7%; *M*, 407. C_7BrF_{13} requires C, 20·45; F, 60·1%; *M*, 411).

(d) Passage of this fluorocarbon, or of perfluorodi*cyclo*hexyl or perfluoro(*iso*propyl*cyclo*hexane), through the tube at 550—600° alone or mixed with one another or with perfluoro-(methyl*cyclo*hexane), gave, in all cases, mixed products from which no pure compounds could be isolated. Dilution of the fluorocarbon with nitrogen effected no improvement. A typical product had b. p. 25—130°, with no flat portions on the distillation curve.

4H-*Tridecafluoro*(*methyl*cyclo*hexane*) *from the* 4-*Chloro-analogue.*—4-Chlorotridecafluoro-(methyl*cyclo*hexane) (186 g.; obtained from *p*-chlorotoluene), in ether (100 c.c.), was added, during 90 min., to a stirred suspension of lithium aluminium hydride (12·5 g.) in ether (200 c.c.). The heat of reaction caused a gentle reflux, and, after the addition, the mixture was refluxed for 3 hr. further. Water was then added cautiously, followed by nitric acid until the precipitates had dissolved, and, after being separated, washed with water, dried ($MgSO_4$), and filtered, the organic layer was fractionally distilled. 4*H*-Tridecafluoro(methyl*cyclo*hexane) (73 g.), b. p. 86·6—88·0° (Found: C, 25·1; H, 0·6; F, 74·9%; *M*, 332), was obtained.

A sample of the chloro-compound made from *p*-chlorobenzotrifluoride, when treated likewise, gave a similar product (44%), b. p. 86·2—88·0° (Found: C, 25·5; H, 0·5; F, 74·0%).

Examination of the three samples of the hydrofluorocarbon by gas–liquid partition chromatography gave two peaks in each case. For the sample derived from the reaction of the fluorocarbon and toluene, the peaks had roughly equal heights. The samples derived ultimately from *p*-chlorotoluene and *p*-chlorobenzotrifluoride gave peaks in the same places, but in both cases the smaller one was only about ¼ of the height of that from the other sample, the larger peaks being almost identical in all cases.

Nonafluoro-4-trifluoromethylcyclohex-1-ene.—4-*H*-Tridecafluoro(methylcyclohexane) (24·0 g.) was boiled under reflux with potassium hydroxide (20 g.) in water (25 c.c.) for 5 hr. After being separated, washed with water, dried (P_2O_5), and filtered, the product was fractionated through a 1′ column. *Nonafluoro-4-trifluoromethylcyclohex-1-ene* (12·0 g.), b. p. 75·4—75·9°, n_D^{20} 1·293 (Found: C, 26·9; F, 72·6%; *M*, 312. C_7F_{12} requires C, 26·9; F, 73·1%; *M*, 312), was obtained. Each of the three samples of the hydrofluorocarbon gave a product with these properties. Gas-chromatographic examination revealed only a single identical peak in each case.

Addition of Halogen to this Olefin.—The olefin described above (1·53 g.) and bromine (0·25 c.c.) were sealed in a hard-glass tube and irradiated by an ultraviolet lamp for 16 hr. After being washed, dried (P_2O_5), and distilled, the product afforded 1 : 2-*dibromononafluoro-4-trifluoromethylcyclohexane* (1·32 g.), b. p. 156—159° (Found: C, 17·9. $C_7Br_2F_{12}$ requires C, 17·8%).

A similar reaction with chlorine gave 1 : 2-*dichlorononafluoro-4-trifluoromethylcyclohexane* (50%), b. p. 129—131° (Found: F, 58·9. $C_7Cl_2F_{12}$ requires F, 59·5%).

Oxidation of the Olefin.—Nonafluoro-4-trifluoromethylcyclohex-1-ene (30·0 g.), potassium permanganate (120 g.), and water (300 c.c.) were heated at 115° for 16 hr. in a rocking autoclave. Isolation by the usual technique (see earlier papers) gave an acidic solid, which, after being dried *in vacuo*, was recrystallised from dry benzene to give the very hygroscopic *perfluoro-(3-methyladipic) acid* (22·1 g.), m. p. 60—61° (Found: C, 24·5; H, 0·9; F, 55·3%; equiv., 172. $C_7H_2O_4F_{10}$ requires C, 24·7; H, 0·6; F, 55·9%; equiv., 170).

Derivatives of Heptafluoro-3-trifluoromethyladipic Acid.—With *S*-benzylthiuronium chloride in concentrated aqueous solution, the acid gave the *di-(S-benzylthiuronium) salt* (from water), m. p. 208° (Found: C, 41·5; H, 3·4; S, 9·7. $C_{23}H_{22}O_4N_4S_2F_{10}$ requires C, 41·1; H, 3·3; S, 9·5%).

The acid (11·0 g.), ethyl alcohol (*ca.* 20 c.c.), and commercial fluorosulphonic acid (1·0 c.c.) were refluxed together for 1 hr. The product was worked up as usual, and, since esterification appeared to be incomplete, it was re-treated as before. Isolation followed by distillation afforded the *diethyl ester* (8·0 g.), b. p. 112°/14 mm., n_D^{12} 1·361 (Found: C, 33·6; H, 2·5; F, 48·0. $C_{11}H_{10}O_4F_{10}$ requires C, 33·3; H, 2·5; F, 48·0%).

Ammonia gas was passed through a solution of the ester in ether. After 16 hr., the precipitate was filtered off and recrystallised from water to give *heptafluoro-3-trifluoromethyladipdiamide* (70%), m. p. 168—169° (Found: C, 24·6; H, 1·2; F, 56·2. $C_7H_4O_2N_2F_{10}$ requires C, 24·9; H, 1·2; F, 56·2%).

Acid derived from each of the three samples of olefin was subjected to these procedures. In each case, the product had the above characteristics, and, in the cases of the solids, no depressions were observed when mixed m. p.s were carried out.

1H : 4H-*Heptafluoro-2-trifluoromethylbutane.*—Heptafluoro-3-trifluoromethyladipic acid was titrated with aqueous potassium hydroxide to pH 5, and the solution obtained was evaporated to dryness. The resultant dipotassium salt (5·3 g.), after 4 hr. in refluxing ethylene glycol (8·0 c.c.), afforded 1H : 4H-*heptafluoro-2-trifluoromethylbutane* (1·7 g.), b. p. 63—65° (Found: C, 23·7; H, 0·8. $C_5H_2F_{10}$ requires C, 23·8; H, 0·8%).

Gas-chromatographic analysis of this compound revealed a single peak only.

Treatment of the compound (0·17 g.) with potassium hydroxide (0·2 g.), in water (0·2 c.c.), at 100° for 14 hr. in a small rocked bomb, effected the elimination of only 0·0036 g. of fluoride ion. When about a stoicheiometric proportion of potassium hydroxide in ethyl alcohol (*ca.* 2N) was used, for 20 min. at 100°, fluoride ion (approx. 2 mol.) was eliminated, but the product was unchanged starting material together with a complex high-boiling residue. After 20 min. at 100° with excess of alcoholic alkali, virtually all of the fluorine had been eliminated from the fluorohydrocarbon.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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Hydrazine. Part X. Salts of Some Aldazines and Ketazines.*

By (Mrs.) E. G. Sohn, R. H. Marks, and W. Pugh.

[Reprint Order No. 5430.]

Simple and complex salts of a variety of aromatic aldazines and ketazines are described. No salts of aliphatic aldazines, and only a few of aliphatic ketazines, could be prepared by similar methods.

Parts II, IV, and VI * describe some complex salts of dimethyl ketazine and certain hydrazones. Shoesmith and Slater had previously reported a chlorostannate of anisaldazine (*J.*, 1925, **127**, 1490). The present work, undertaken to survey the salt-forming properties of azines in general, has resulted in the preparation of halides, sulphates, halogeno-antimonites, -bismuthites, -stannates, and -platinates of a variety of azines. The following points emerge: (1) Aromatic aldazines and ketazines yielded halides, sulphates, and complex salts. (2) Aliphatic ketazines gave salts less readily; no simple salts were obtained; dimethyl ketazine yielded complex salts but its homologues, under comparable conditions, formed salts of the corresponding hydrazones instead, thereby confirming observations made in Parts II, IV, and VI (*locc. cit.*). (3) Aliphatic aldazines have yielded no crystalline salts; in some cases, oily products were obtained at −50° or below (which decomposed rapidly at room temperature) and, in other cases, crystalline products of variable composition showing varying degrees of polymerisation. (4) " Mixed " azines, containing 1 mol. of each of aromatic aldehyde and acetone condensed per mol. of hydrazine, gave salts most readily. (That these were not salts of Mannich bases is shown on p. 1755.)

The halides and sulphates were obtained, with the single exception of salicylaldazine hydrobromide, only under strictly anhydrous conditions; they are readily hydrolysed in aqueous solution. The same was true of the chloro-complexes; the bromo- and iodo-complexes, on the other hand, are less soluble and more stable and were generally obtained by adding the concentrated acid to the azine and metal salt in nitrobenzene solution. The complex platinates undergo self-reduction in aqueous media and were also best prepared from non-aqueous media.

Experimental

Analytical Methods.—The methods of analysis employed were those previously reported (Part VI, *loc. cit.*; *J. Appl. Chem.*, 1954, **4**, 47), but it was essential to remove aldehyde and ketone as a preliminary to analysis by boiling with 5N-hydrochloric acid (for hydrazine, sulphate, bismuth, and tin) or with 2N-sulphuric acid (for halogen and antimony). Tin was first separated as sulphide because direct precipitation of hydrated oxide gave low results.

General Methods of Preparation.—Although the ketazinium salts described in previous papers were made direct from the ketone, the salts now to be described were best prepared from the azine. The salts of salicylaldazine in particular were liable to contain free salicylaldazine, and fractional crystallisation or extraction with hot solvent was found necessary. The yields were in most cases 40—90%.

(*a*) Hydrochlorides and chloro-metallic complex salts: hydrogen chloride was passed through solutions of the azine, or of azine and metal halide, in nitrobenzene, ether, or xylene; in a few instances, nitrobenzene solutions of azine hydrochloride and metal chloride were mixed.

(*b*) Bromo- and iodo-metallic complex salts: the azine in nitrobenzene was mixed with the metal bromide or iodide in nitrobenzene, ether, or xylene, and excess of hydrobromic acid (48%) or hydriodic acid (57%) was added. Crystals separated at the interface.

(*c*) Complex platinates: chloroplatinic acid in ether, or bromoplatinic acid in *n*-butyl alcohol, was added to the azine and a small amount of the corresponding aldehyde or ketone in ether.

(*d*) Sulphates: an equivalent quantity of sulphuric acid (98%) in ether solution (2%) was added to the azine in ether or xylene.

(*e*) " Mixed " azines: molecular proportions of aromatic aldehyde and hydrazine hydrate (95%) were boiled with acetone and excess of hydrobromic or hydriodic acid; or the hydrazone was simply dissolved in acetone. The iodide (Table 3) was also made by adding hydriodic acid to dimethyl ketazine in benzaldehyde at 0°.

* Parts II, IV, VI, IX, *J.*, 1953, 354, 2491, 3445; 1954, 2429.

TABLE 1. *Halogeno-antimonites and -bismuthites of benzaldazine, salicylaldazine, and anisaldazine,* $(R{:}N{\cdot}N{:}R)HMX_4$

	Compound * R	MX_4	M. p.	Formula	Found (%) C	H	N_2H_4	M	X	Required (%) C	H	N_2H_4	M	X	Method †
(1)	$C_6H_5{\cdot}CH$	$SbCl_4$	156—157°	$C_{14}H_{12}N_2SbCl_4$	35·2	2·7	6·8	26·1	30·7	35·5	2·7	6·8	25·8	30·2	*a* (nb)
(2)	o-$C_6H_4(OH){\cdot}CH$	$SbCl_4$	175—182	$C_{14}H_{12}O_2N_2SbCl_4$	33·7	2·5	6·2	24·1	28·1	33·3	2·6	6·3	24·2	28·1	*a* (nb)
(3)	p-$C_6H_4(OMe){\cdot}CH$	$SbCl_4$	198—200	$C_{16}H_{17}O_2N_2SbCl_4$	36·1	3·5	6·2	22·9	26·5	36·0	3·2	6·0	22·9	26·7	*a* (nb)
(4)	$C_6H_5{\cdot}CH$	$SbBr_4$	179—180	$C_{14}H_{12}N_2SbBr_4$	25·9	2·2	4·8	18·7	49·4	25·8	2·0	4·9	18·7	49·2	*a* (nb)
(5)	o-$C_6H_4(OH){\cdot}CH$	$SbBr_4$	192—193	$C_{14}H_{12}O_2N_2SbBr_4$	24·7	1·9	4·8	17·9	47·0	24·6	1·9	4·7	17·9	46·9	*b* (nb)
(6)	p-$C_6H_4(OMe){\cdot}CH$	$SbBr_4$	216—218	$C_{16}H_{17}O_2N_2SbBr_4$	27·6	2·7	4·5	17·1	45·0	27·0	2·4	4·5	17·2	45·0	*b* (nb)
(7)	$C_6H_5{\cdot}CH$	SbI_4	173—190	$C_{14}H_{12}N_2SbI_4$	20·8	1·6	3·6	15·0	60·7	20·1	1·6	3·8	14·6	60·5	*b* (ether and xylene)
(8)	o-$C_6H_4(OH){\cdot}CH$	SbI_4	211—212	$C_{14}H_{12}O_2N_2SbI_4$	19·1	1·8	3·6	13·9	58·1	19·3	1·5	3·7	14·0	58·4	*b* (nb)
(9)	p-$C_6H_4(OMe){\cdot}CH$	SbI_4	214—215	$C_{16}H_{17}O_2N_2SbI_4$	22·0	2·1	3·5	13·9	56·5	21·6	1·9	3·6	13·6	56·5	*b* (nb)
(10)	$C_6H_5{\cdot}CH$	$BiCl_4$	200—206	$C_{14}H_{12}N_2BiCl_4$	29·6	2·4	5·7	37·4	25·5	30·0	2·3	5·7	37·3	25·4	*a* (nb)
(11)	o-$C_6H_4(OH){\cdot}CH$	$BiCl_4$	213—220	$C_{14}H_{12}O_2N_2BiCl_4$	28·0	2·6	5·5	35·2	24·3	28·4	2·2	5·4	35·3	24·0	*a* (nb)
(12)	p-$C_6H_4(OMe){\cdot}CH$	$BiCl_4$	236—237	$C_{16}H_{17}O_2N_2BiCl_4$	30·9	3·1	5·2	33·6	22·9	31·0	2·7	5·2	33·7	22·9	*a* (nb)
(13)	$C_6H_5{\cdot}CH$	$BiBr_4$	229—234	$C_{14}H_{12}N_2BiBr_4$	22·4	1·7	4·3	27·7	43·8	22·8	1·8	4·3	28·3	43·4	*b* (nb)
(14)	o-$C_6H_4(OH){\cdot}CH$ ‡	$BiBr_4$	*ca.* 227	$C_{14}H_{12}O_2N_2BiBr_4$	—	—	4·6	—	40·3	—	—	4·2	—	41·6	*b* (nb)
(15)	p-$C_6H_4(OMe){\cdot}CH$	$BiBr_4$	244—245	$C_{16}H_{17}O_2N_2BiBr_4$	25·3	2·4	4·2	26·2	40·6	24·3	2·2	4·1	26·2	40·5	*b* (xylene)
(16)	$C_6H_5{\cdot}CH$	BiI_4	228—230	$C_{14}H_{12}N_2BiI_4$	17·9	1·7	3·8	22·4	55·2	18·2	1·4	3·5	22·6	54·8	*b* (nb)
(17)	o-$C_6H_4(OH){\cdot}CH$	BiI_4	246—253	$C_{14}H_{12}O_2N_2BiI_4$	17·4	1·6	3·3	21·6	—	17·5	1·4	3·3	21·8	—	*b* (nb)
(18)	p-$C_6H_4(OMe){\cdot}CH$	BiI_4	235—238	$C_{16}H_{17}O_2N_2BiI_4$	19·6	1·6	3·1	20·8	51·0	19·5	1·7	3·2	21·2	51·5	*b* (nb)

* Colour (and form) of crystals: (1) pale yellow; (2) yellow; (3) orange; (4) yellow; (5) yellow; (6) orange; (7) orange-red; (8) orange-red; (9) orange-red; (10) yellow needles; (11) orange; (12) orange; (13) yellow; (14) orange; (15) orange; (16)—(18) red.
† See "General Methods of Preparation" (p. 1753); nb = nitrobenzene.
‡ After repeated crystallisation, and washing with hot nitrobenzene, still contained some salicylaldazine.

TABLE 2. *Halogeno-stannates and -platinates of some azines and hydrazones,* $(R{:}N{\cdot}N{:}R')_2H_2MX_6$.

	Compound * R	R′	MX_6	M. p.	Formula	Found (%) C	H	N_2H_4	M	X	Required (%) C	H	N_2H_4	M	X	Method †
(1)	$C_6H_5{\cdot}CH$		$SnCl_6$	217—225°	$(C_{14}H_{12}N_2)_2SnCl_6$	45·3	3·9	8·6	15·4	27·9	44·8	3·5	8·6	15·8	28·4	*a* (ether)
(2)	o-$C_6H_4(OH){\cdot}CH$		$SnCl_6$	212—220	$(C_{14}H_{12}O_2N_2)_2SnCl_6$	40·7	3·1	7·9	15·0	26·5	41·4	3·2	7·9	14·7	26·2	*a* (xylene)
(3)	$C_6H_5{\cdot}CH$		$SnBr_6$	218—225	$(C_{14}H_{12}N_2)_2SnBr_6$	32·4	2·6	6·3	11·6	46·7	33·1	2·6	6·3	11·6	47·2	*b* (nb)
(4)	p-$C_6H_4(OMe){\cdot}CH$		$SnBr_6$	240—242	$(C_{16}H_{17}O_2N_2)_2SnBr_6$	33·9	2·9	5·6	10·5	42·2	33·9	3·0	5·6	10·4	42·3	*b* (nb)
(5)	$C_6H_5{\cdot}CH$		$PtBr_6$	188—189	$(C_{14}H_{12}N_2)_2PtBr_6$	—	—	5·9	18·7	44·1	—	—	5·9	17·9	43·8	*c*
(6)	CMePh		$PtBr_6$	190—191	$(C_{16}H_{17}N_2)_2PtBr_6$	—	—	5·6	17·1	42·5	—	—	5·7	17·3	42·5	*c*
(7)	$C_6H_5{\cdot}CH$	CMePh	$PtBr_6$	214—216	$(C_{15}H_{14}N_2)_2PtBr_6$	—	—	5·0	15·1	37·4	—	—	5·0	15·2	37·4	*c*
(8)	CMe_2		$PtBr_6$	82—84	$(C_9H_{12}N_2)_2PtBr_6$	—	—	6·9	22·9	54·5	—	—	7·1	21·7	53·3	*c*
(9)	CMe_2		$PtCl_6$	157—158 (decomp.)	$(C_9H_{12}N_2)_2PtCl_6$	—	—	10·5	31·4	33·6	—	—	10·1	32·2	35·1	*c*
(10)	CEt_2	H	$PtBr_6$	decomp.	$(C_9H_{12}N_2)_2PtBr_6$	—	—	7·3	21·7	56	—	—	7·3	22·3	54·7	*c*
(11)	CEt_2	H	$PtCl_6$	187—188	$(C_9H_{12}N_2)_2PtCl_6$	—	—	10·4	34·5	34·8	—	—	10·5	32·1	35·1	*c*

* Colour, etc., of crystals: (1) pale yellow powder; (2)—(4) yellow crystalline powder; (5) orange powder; (6) and (7) red, birefracting straight extinction; (8) red, birefracting; (9) orange, birefracting; (10) red powder; (11) orange powder.
† See "General Methods of Preparation" (p. 1753); (nb) = nitrobenzene.

(*f*) Hydrobromic acid (48%) was added to a hot saturated solution of the azine in nitrobenzene.

General Properties of the Salts.—Apart from the complex platinates, which are red, the aldazinium salts show the expected gradation in colour and m. p. The chloro-salts are lightly coloured, the bromo-salts yellow or orange, and the iodo-salts red; the m. p. rises with increasing complexity of the base for any one anion, with increasing atomic weight of the halogen for the same base and metal, and with increasing atomic weight of the metal for the same base and halogen. The simple salts and the chloro-complexes are readily hydrolysed in water, smelling of aldehyde or ketone in moist air, but the bromo- and the iodo-complexes, especially, are decomposed with difficulty by boiling hydrochloric acid. The complex platinates undergo self-reduction, slowly in water and rapidly in alkali, to platinum and nitrogen. They are insoluble in *cyclo*hexane, ether, and xylene, and sparingly soluble in nitrobenzene, dioxan, and pyridine.

Unsuccessful Attempts to make Salts.—Attempts to make simple salts of acetaldazine, dimethyl ketazine, di-*n*-propyl ketazine, and di-*n*-butyl ketazine failed. Impure chlorides and sulphates were obtained from *n*-butaldazine and *n*-propaldazine. Propaldazine and butaldazine gave no salts with the complex acids used, but acetaldazine and crotonaldazine gave crystalline halogeno-stannates, -antimonites, and -bismuthites of variable composition; the equivalent weight of the base in these products was high, indicating polymerisation.

N-*o*-*Nitrobenzylidene*-N′-*isopropylidenehydrazinium Bromide.*—This *salt* separated as creamy white crystals, darkening with age, m. p. 156—158°, when hydrobromic acid (48%) was added to *o*-nitrobenzaldehyde hydrazone in acetone (Found: C, 41·9; H, 3·8; N_2H_4, 11·0; Br, 27·6. $C_{10}H_{12}O_2N_3Br$ requires C, 42·0; H, 4·2; N_2H_4, 11·0; Br, 27·4%). A sample of this salt was made into a paste with potassium carbonate and water and extracted with ether. The free base, isolated in the usual way, had m. p. 67°, undepressed on mixing with an authentic specimen. (This proved that it was not a salt of a Mannich base.)

Bis-(NN-*di*-o-*nitrobenzylidenehydrazinium*) *Hexachlorostannate.*—A greyish crystalline powder, m. p. 183—190° (blackening at 180), of the above-named *salt* was precipitated on treating *o*-nitrobenzaldazine (2 mols., in hot, dry xylene) with stannic chloride (1 mol., in nitrobenzene) and hydrogen chloride [Found: C, 37·0; H, 3·0; N_2H_4, 6·7; Cl, 22·7; Sn, 12·8. $(C_{14}H_{11}O_4N_3)_2SnCl_6$ requires C, 36·2; H, 2·4; N_2H_4, 6·9; Cl, 22·9; Sn, 12·8%].

Tables 1, 2, and 3 give the other salts that have been characterised.

TABLE 3. *Halides and sulphates of some aldazines and ketazines,* (R:N·N:R′)HX.

	Compound * R	R′	X	M. p.	Formula	Found (%) C	N_2H_4	X †	Required (%) C	N_2H_4	X †	Method
(1)	C_6H_5·CH		HSO_4	160—161°	$C_{14}H_{12}N_2HSO_4$	53·4	10·5	31·7	54·8	10·5	31·4	*d* (ether)
(2)	*o*-C_6H_4(OH)·CH		Br	211—213	$C_{14}H_{12}O_2N_2Br$	50·9	9·9	24·9	52·3	10·0	24·9	*f*
(3)	*o*-C_6H_4(OH)·CH		HSO_4	178—179	$C_{14}H_{12}O_2N_2HSO_4$	49·7	9·5	28·3	49·7	9·5	28·4	*d* (xylene)
(4)	*p*-C_6H_4(OMe)·CH		HSO_4	202—203	$C_{16}H_{17}O_2N_2HSO_4$	52·1	8·7	26·3	52·5	8·7	26·2	*d* (ether)
(5)	CMePh		Cl	132—134	$C_{16}H_{17}N_2Cl$	—	11·8	13·4	—	11·7	13·0	*a* (ether)
(6)	CMePh		HSO_4	125—126	$C_{16}H_{17}N_2HSO_4$	—	9·8	29·4	—	9·6	28·8	*d* (ether)
(7)	CPh_2		Cl	166—168	$C_{26}H_{21}N_2Cl$	—	8·1	9·0	—	8·1	9·2	*a* (ether)
(8)	*o*-C_6H_4(OH)·CH	CMe_2	Br	177—178	$C_{10}H_{13}ON_2Br$	46·8	12·5	31·2	46·7	12·5	31·1	*e* (acetone)
(9)	C_6H_5·CH	CMe_2	Br	135—136	$C_{10}H_{13}N_2Br$	49·6	13·2	33·2	49·8	13·3	33·2	*e* (acetone)
(10)	C_6H_5CH	CMe_2	I	107—108	$C_{10}H_{13}N_2I,H_2O$ ‡	38·8	10·3	41·3	39·2	10·5	41·5	*e* (acetone)

* Colour, etc., of crystals: (1) yellow; (2)—(3) yellow plates; (4) yellow powder; (5)—(7) white; (8) pink, monoclinic; (9) white; (10) yellow. † Here, X = halogen or SO_4 (not HSO_4).
‡ Found: Loss at 56°/15 mm., 5·5. Required: H_2O, 5·9%.

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UNIVERSITY OF CAPE TOWN.

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Synthetic Plant Hormones. Part III. Aryloxymethylphosphonates.*

By (Miss) M. H. Maguire and G. Shaw.

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Several aryloxymethylphosphonates (I; R = Et, R′ = H) have been prepared by the reaction of a number of sodium aryloxides with the iodo-ester (II; R = R′ = Et), which proceeds by way of the half-ester (II; R = Et, R′ = H). The products were readily hydrolysed by concentrated hydrochloric acid to the diacids (I; R = R′ = H). Preliminary biological evaluations of some of these compounds are briefly discussed.

Previous communications in this series have been concerned with the preparation of analogues of the phenoxyacetic acid series of plant hormones, in particular with variation in the aliphatic side chain. The results indicated that only those compounds which by hydrolytic or oxidative processes (but not reductive, *e.g.*, aryl glucosides) could give rise to a phenoxyacetic acid, were active, and that activity was closely associated with that of the corresponding acid. Moreover, with the possible exception of the 2 : 4-dichlorophenoxyacetaldehyde sodium hydrogen sulphite adduct, no enhanced translocation or persistence of the compounds in the plants was observed. The failure of phenoxyacetic acid activity to persist in plant tissue is undoubtedly related to the rapid loss of the carboxyl group (as carbon dioxide), as has been demonstrated by using labelled molecules (Weintraub, Brown, Fields, and Rohan, *Plant Physiol.*, 1952, **27**, 292).

We therefore considered it of interest to attempt the preparation of compounds in which the carboxyl group in chloroaryloxyacetic acids was replaced by some other acidic group which could not be converted simply into a carboxyl group. The synthesis of one such group of compounds, aryloxymethylphosphonic acids (I), is described in this paper (for a note see Maguire, Shaw, and Greenham, *Chem. and Ind.*, 1953, 668); preliminary experiments on the preparation of analogous sulphonates were abandoned after this had been reported by Barber, Cottrell, Fuller, and Green (*J. Appl. Chem.*, 1953, **3**, 253).

$ArO{\cdot}CH_2{\cdot}PO(OR)(OR')$ (I) $\qquad$ $I{\cdot}CH_2{\cdot}PO(OR)(OR')$ (II)

Aryloxymethylphosphonates (I) have not hitherto been described; the closest reported analogues appear to be 2-phenoxyethylphosphonic acid $PhO{\cdot}CH_2{\cdot}CH_2{\cdot}PO(OH)_2$ (Mikhailova, *Uchenye Zapiski Kazan. Gosudarst Univ. im V.I. Ul'yanova Lenina* **101**, No. 3, *Sbornik Studencheskikh Rabot*, No. 2, 58, 1941; *Chem. Abs.*, 1946, **40**, 555) and diethyl benzyloxymethylphosphonate $Ph{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}PO(OEt)_2$ (Abramov, Sergeeva, Chelpanova, *Zhur. obschei Khim.*, 1944, **14**, 1030; *Chem. Abs.*, 1947, **41**, 700); both compounds were prepared by the Arbuzov reaction (Kosolapoff, " Organo-Phosphorus Compounds," Wylie, New York, 1950, p. 121), namely, reaction of an alkyl or aralkyl halide and a trialkyl phosphite: $RX + P(OR')_3 \longrightarrow R{\cdot}PO(OR')_2 + R'X$. The synthesis of aryloxymethylphosphonates by this reaction would require as intermediates the ω-halogenoanisoles $ArO{\cdot}CH_2X$ and until recently (Barber *et al.*, *loc. cit.*) such compounds were unknown and our experiments were then almost complete. Other possible routes to the phosphonic acids included (1) the reaction of a halogenomethylphosphonate (II) and a sodium aryloxide and (2) an extension of a recent reaction (Clayton and Jensen, *J. Amer. Chem. Soc.*, 1948, **70**, 3880; Graf, *Chem. Ber.*, 1952, **85**, 9) whereby oxidative phosphorylation of *cyclo*hexane occurs with phosphorus trichloride in a current of dry oxygen: $3C_6H_{12} + 2PCl_3 + O_2 \longrightarrow C_6H_{11}{\cdot}POCl_2 + (C_6H_{11})_2POCl$. The first of these methods seemed the most promising, although the halogen atom in halogenomethylphosphonates is known to be very unreactive; nevertheless it has been replaced by the amino (Kabachnik and Medved, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1950, 635; *Chem. Abs.*, 1951, **45**, 8444) and the hydroxyl group (Kabachnik and Shepeleva, *ibid.*, 1951, 185; *Chem. Abs.*, 1951, **45**, 10,191) under drastic conditions.

* Part II, *J.*, 1954, 3669.

Diethyl iodomethylphosphonate (II; R = R′ = Et) failed to react with sodium 2 : 4-dichlorophenoxide in boiling ethanol but some reaction occurred in boiling toluene (see Experimental section). A rapid reaction occurred, however, when dry sodium 2 : 4-dichlorophenoxide (1·5 mols.) and the iodo-ester (1 mol.) were heated together to 160°, there being no apparent decomposition; the products were ethyl hydrogen 2 : 4-dichlorophenoxymethylphosphonate (as I; R = Et, R′ = H) and 2 : 4-dichlorophenetole; an increased yield of the half-ester was obtained when the molar ratios were increased to 2 : 1. It was of interest to determine whether de-esterification or replacement of halogen occurred first, and so reactions were carried out with 1 : 1 and 1 : 2 molar ratios of phenoxide to ester. The 1 : 1 ratio gave a mixture of *o*-chlorophenetole, ethyl hydrogen *o*-chlorophenoxymethylphosphonate, and ethyl hydrogen iodomethylphosphonate (II; R = Et, R′ = H), and the 1 : 2 ratio gave only the phenetole (in increased yield) and the iodo-ester (II; R = Et, R′ = H). These results clearly indicated that de-esterification occurred first, and the reaction scheme may be summarised:

(1) $ArONa + I{\cdot}CH_2{\cdot}PO(OEt)_2 \longrightarrow I{\cdot}CH_2{\cdot}PO(OEt)(ONa) + ArOEt$

(2) $ArONa + I{\cdot}CH_2{\cdot}PO(OEt)(ONa) \longrightarrow ArO{\cdot}CH_2{\cdot}PO(OEt)(ONa) + NaI$

The half-esters (I; R = Et, R′ = H) were singularly resistant to alkaline hydrolysis, being almost unaffected by 50% sodium hydroxide solution at 140° or an excess of a sodium aryloxide. The diacids (I; R = R′ = H) were, however, readily and quantitatively prepared by boiling the half-esters for a short time with concentrated hydrochloric acid although the analogous compounds, diethyl 2-phenoxyethylphosphonate and diethyl benzyloxymethylphosphonate are reported to undergo ether fission with 10% hydrochloric acid at 120°, whereas hydrolysis of the former compound with 10% sodium hydroxide solution at 150—160° was quantitative (Mikhailova *et al.*, and Abramov *et al.*, *locc. cit.*).

By the above methods the 2-, 3-, and 4-chloro-, 2 : 4-dichloro-, 2 : 4 : 5- and 2 : 4 : 6-trichloro-phenoxymethylphosphonates, together with the ethyl hydrogen esters and the unsubstituted diacid, were prepared.

Similar attempts to prepare the unsubstituted half-ester (I; R = Et, R′ = H) gave an acidic oil; distillation of this substance *in vacuo* gave a neutral distillate, apparently isomeric with the half-ester, and a residue of the diacid. The latter compound was also obtained by hydrolysis of the crude half-ester and of the neutral liquid.

The results of preliminary biological tests on a few of these compounds have been published (Greenham, *Austral. J. Sci.*, 1953, **16**, 66); in both the split-pea, and pea-epicotyl tests, ethyl hydrogen 2 : 4-dichlorophenoxymethylphosphonate had slight but significant auxin properties. In addition the latter compound and also ethyl hydrogen 2-chloro- (but not 4-chloro-)phenoxymethylphosphonate significantly increased the dry weights of wheat-seedling tops, although they were without effect on germination. On the other hand the corresponding 2 : 4 : 5-trichloro-half-ester reduced the dry weight of rape-seedling tops. The weight effects appear to be a function of the phosphonate group since methylphosphonic acid had a similar effect at low concentrations.

Experimental

Triethyl phosphite was prepared by Ford-Moore and Williams's method (*J.*, 1947, 1465) and diethyl iodomethylphosphonate by the Arbuzov reaction (Arbuzov and Kushkova, *J. Gen. Chem., U.S.S.R.*, 1936, **6**, 283; Ford-Moore and Williams, *loc. cit.*) from triethyl phosphite and methylene iodide. The sodium aryloxides were prepared by the addition of sodium to a solution of the phenol in boiling toluene; the salts were filtered off, washed with benzene, and dried *in vacuo*.

Reaction of Sodium 2 : 4-Dichlorophenoxide and Diethyl Iodomethylphosphonate.—(a) *In ethanol.* A solution of sodium 2 : 4-dichlorophenoxide (3·3 g.) and diethyl iodomethylphosphonate (5 g.) in ethanol (150 ml.) was boiled for 24 hr. The solution was evaporated to dryness and the residual paste extracted with ether, leaving unchanged phenoxide (3·1 g.); evaporation of the ether and distillation of the residue *in vacuo* gave the iodo-ester (4 g.), b. p. 130—134°/5 mm.

(b) *In toluene.* Diethyl iodomethylphosphonate (20 g.) was added to a suspension of

sodium 2 : 4-dichlorophenoxide (13·3 g.) in boiling toluene (300 ml.); a clear solution was obtained immediately and this was boiled under reflux for 24 hr. The cooled toluene solution was filtered from a trace of solid and extracted with water (3 × 30 ml.); the aqueous solution was acidified with hydrochloric acid and extracted with ether (3 × 30 ml.); evaporation of the dried extract gave an oil (4·2 g.) with a strong phenolic odour which could not be satisfactorily purified. The toluene solution was distilled *in vacuo*, to give a fraction (6·2 g.), b. p. 90—100°/5 mm., with a phenetole-like odour, and diethyl iodomethylphosphonate (6·5 g.), b. p. 130—134°/5 mm. The first fraction was redistilled several times at atmospheric pressure and finally had b. p. 236—238° corresponding to 2 : 4-dichlorophenetole, b. p. 236—238° (Fischer, *Annalen Suppl.*, 1870, **7**, 183, gives b. p. 236—238°) (Found: C, 49·8; H, 3·95. Calc. for $C_8H_8OCl_2$: C, 50·3; H, 4·2%).

(c) A mixture of sodium 2 : 4-dichlorophenoxide (5 g.) and diethyl iodomethylphosphonate (5 g.) was heated at 160° (bath), whereupon a reaction commenced, then the temperature was kept at 160—170° for 1 hr. The viscous pale brown product was stirred with water (50 ml.), giving an emulsion which was extracted with benzene (3 × 20 ml.); evaporation of the benzene and distillation of the residue gave 2 : 4-dichlorophenetole (1·7 g.), b. p. 238°. The aqueous solution was acidified with hydrochloric acid and extracted with ether (5 × 30 ml.); evaporation of the ether left an oil which soon crystallised; *ethyl hydrogen 2 : 4-dichlorophenoxymethylphosphonate* (2·5 g.) separated from benzene–light petroleum as needles, m. p. 79—81° (Found: C, 37·95; H, 3·8%; equiv., 283·5. $C_9H_{11}O_4Cl_2P$ requires C, 37·9; H, 3·9%; equiv., 285). The half-ester (1 g.) and concentrated hydrochloric acid (8 ml.) were boiled together for 4 hr. The solution was evaporated to dryness to give a crystalline residue; *2 : 4-dichlorophenoxymethylphosphonic acid* (0·9 g.) separated from ethyl acetate–light petroleum as plates, m. p. 141—143° (Found: C, 32·55; H, 2·8. $C_7H_7O_4Cl_2P$ requires C, 32·7; H, 2·75%); a solution of the acid in ether with *n*-pentylamine gave the *di-n-pentylammonium salt* which crystallised from ethanol–ether as needles, m. p. 221—223° (Found: C, 47·35; H, 7·55; N, 6·5. $C_7H_7O_4Cl_2P,2C_5H_{13}N$ requires C, 47·35; H, 7·7; N, 6·5%).

Reaction of Sodium o-Chlorophenoxide and Diethyl Iodomethylphosphonate.—(*a*) A mixture of sodium *o*-chlorophenoxide (7 g., 1 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) was kept at 160—170° (bath) for 1 hr. (reaction commenced at 160°). The cooled mixture was stirred with water (50 ml.), and the resultant emulsion was extracted with benzene (3 × 20 ml.); evaporation of the dried benzene solution and distillation of the residue gave *o*-chlorophenetole (3 g.), b. p. 208° (Kurbatow, *Annalen*, 1875, **176**, 39, gives b. p. 208—208·5°) (Found: C, 61·55; H, 5·85. Calc. for C_8H_9OCl: C, 61·35; H, 5·8%), diethyl iodomethylphosphonate (1·3 g.), b. p. 130°/5 mm., and a tarry residue (1·4 g.). The aqueous solution was acidified with concentrated hydrochloric acid and saturated with sodium chloride, then extracted with ether (3 × 25 ml.). The ethereal solution was extracted with 5% sodium hydrogen carbonate solution (25 ml.), and the extract acidified and saturated with sodium chloride, then extracted with ether (3 × 20 ml.); evaporation of the dried extracts gave an acidic gum (4·8 g.) which when stirred with benzene–*cyclo*hexane gave *ethyl hydrogen o-chlorophenoxymethylphosphonate* (0·2 g.) which crystallised from carbon tetrachloride–light petroleum as laths, m. p. 86—88° (Found: C, 43·05; H, 4·75. $C_9H_{12}O_4ClP$ requires C, 43·15; H, 4·8%). The aqueous solutions were combined and again extracted with ether (5 × 25 ml.); evaporation of the ether gave an acidic oil which crystallised when set aside; *ethyl hydrogen iodomethylphosphonate* (1·5 g.) crystallised from carbon tetrachloride–light petroleum as plates m. p. 46—49° (Found: C, 14·65; H, 3·1. $C_3H_8O_3IP$ requires C, 14·4; H, 3·2%). A solution of the ester (1·5 g.) in concentrated hydrochloric acid (10 ml.) was boiled under reflux for 2½ hr., then evaporated to dryness on a water-bath, to leave a deliquescent crystalline solid (1·3 g.). An ethereal solution of the solid with *n*-pentylamine precipitated *di-n-pentylammonium iodomethylphosphonate* which crystallised from propan-2-ol as plates, m. p. 162° (softening from 148°) (Found: C, 33·4; H, 7·5; N, 6·85. $CH_4O_3IP,2C_5H_{13}N$ requires C, 33·35; H, 7·65; N, 7·05%).

(*b*) Sodium *o*-chlorophenoxide (14 g., 2 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) were heated together as above, to give *o*-chlorophenetole (5·5 g.) and ethyl hydrogen *o*-chlorophenoxymethylphosphonate (7·7 g.), m. p. 87°. A solution of the ester (1 g.) in concentrated hydrochloric acid (8 ml.) was boiled under reflux for 3 hr. When the solution was cooled a crystalline precipitate separated; *o-chlorophenoxymethylphosphonic acid* (0·7 g.) crystallised from acetone–benzene–carbon tetrachloride as plates, m. p. 133—134° (Found: C, 37·5; H, 3·7. $C_7H_8O_4ClP$ requires C, 37·75; H, 3·6%). A further quantity of the acid (0·2 g.) was obtained by evaporation of the aqueous hydrolysis solution.

(*c*) A mixture of sodium *o*-chlorophenoxide (6 g., 1 mol.) and diethyl iodomethylphosphonate

(22 g., 2 mol.) was kept at 160—170° (bath) for 1½ hr. The product was treated with water (50 ml.), and the resulting emulsion extracted with benzene (4 × 30 ml.); evaporation of the benzene and distillation of the residue *in vacuo* gave *o*-chlorophenetole (4 g.), b. p. 103—104°/26 mm., and diethyl iodomethylphosphonate (7·6 g.), b. p. 110—112°/3 mm. The aqueous solution was acidified with hydrochloric acid, saturated with sodium chloride, and thoroughly extracted with ether; evaporation of the ether gave an oil (8·1 g.) which soon crystallised; ethyl hydrogen iodomethylphosphonate separated from carbon tetrachloride–light petroleum as plates (5·5 g.), m. p. 46—49°.

Reaction of Sodium 2 : 4 : 5-*Trichlorophenoxide and Diethyl Iodomethylphosphonate*.—A mixture of sodium 2 : 4 : 5-trichlorophenoxide (20·5 g., 1 mol.) and diethyl iodomethylphosphonate (13 g., 1 mol.) was kept at 190—200° (bath) for 1 hr. The cold semi-solid product was treated with water (50 ml.). A crystalline solid separated which was washed with water and benzene; hydrated *sodium ethyl* 2 : 4 : 5-*trichlorophenoxymethylphosphonate* (10·1 g.) crystallised from propan-2-ol as needles, m. p. 191—193° (Found: C, 28·05; H, 3·6. $C_9H_9O_4Cl_3NaP,2\frac{1}{2}H_2O$ requires C, 27·95; H, 3·65%). The sodium salt (10 g.) was dissolved in warm water (300 ml.), and the solution acidified with hydrochloric acid, saturated with sodium chloride, and extracted with ether (4 × 100 ml.); evaporation of the solvent gave *ethyl hydrogen* 2 : 4 : 5-*trichlorophenoxymethylphosphonate* (9·1 g.) which crystallised from carbon tetrachloride as needles, m. p. 97° (Found: C, 33·85; H, 3·15%; equiv., 317. $C_9H_{10}O_4ClP$ requires C, 33·85; H, 3·15%; equiv., 319·5). The aqueous filtrate from the first-mentioned reaction was extracted with a further quantity of benzene (3 × 50 m.); evaporation of the solvent and distillation of the residue gave 2 : 4 : 5-trichlorophenetole (9·2 g.), b. p. 256—264°, m. p. 42—43° (Agfa, D.-R.P. 411,052/1924, gives m. p. 95°) (Found: C, 42·7; H, 3·05. Calc. for $C_8H_7OCl_3$: C, 42·6; H, 3·15%). The aqueous solution was acidified with hydrochloric acid and extracted with ether, to give a further quantity of the half-ester (2 g.), m. p. 96—97°; a solution of this (1 g.) in concentrated hydrochloric acid (8 ml.) was boiled under reflux for 4 hr.; the solution was cooled, to give a crystalline precipitate; 2 : 4 : 5-*trichlorophenoxymethylphosphonic acid hemihydrate* (0·9 g.) separated from acetone–benzene as needles, m. p. 179—180° (Found: C, 27·65; H, 2·35. $C_7H_6O_4Cl_3P,\frac{1}{2}H_2O$ requires C, 28·0; H, 2·35%).

Similar experiments led to: *sodium ethyl* p-*chlorophenoxymethylphosphonate* (4·7 g. from 14 g. of the phenoxide and 13 g. of diethyl iodomethylphosphonate), needles (from propan-2-ol), m. p. 286—287° (Found: C, 39·75; H, 4·1. $C_9H_{11}O_4ClNaP$ requires C, 39·65; H, 4·05%) (the acid failed to crystallise); *p*-chlorophenetole (4·2 g.), b. p. 205—208° (Kurbatow, *loc. cit.*, gives b. p. 210—212°), and p-*chlorophenoxymethylphosphonic acid* (0·8 g. from 1·5 g. of the sodium salt of the half ester), plates (from acetone–carbon tetrachloride), m. p. 155—156° (Found: C, 37·6; H, 3·5%); S-*benzylthiuronium ethyl* m-*chlorophenoxymethylphosphonate* (8·7 g. of crude acid from 11·4 g. of the phenoxide and 10·5 g. of diethyl iodomethylphosphonate), needles (from ethyl acetate–light petroleum), m. p. 137—138° (Found: C, 48·8; H, 5·25; N, 6·6. $C_9H_{13}O_4ClP,C_8H_{10}N_2S$ requires C, 49·0; H, 5·3; N, 6·7%) (the acid and its sodium salt failed to crystallise); *m*-chlorophenetole (4 g.), b. p. 200° (Reverdin and Eckhard, *Ber.*, 1899, **32**, 2626, give b. p. 191—192°/728 mm.), and *di*-n-*pentylammonium* m-*chlorophenoxymethylphosphonate hydrate* (the acid failed to crystallise) as needles (from propan-2-ol), m. p. 160—180° (decomp.) (Found: C, 48·95; H, 8·45; N, 6·4. $C_7H_6O_4ClP,2C_5H_{13}N,H_2O$ requires C, 49·2; H, 8·75; N, 6·75%); *ethyl hydrogen* 2 : 4 : 6-*trichlorophenoxymethylphosphonate* (7·9 g. from 20·5 g. of the phenoxide and 13 g. of diethyl iodomethylphosphonate at 185—201°), needles (from carbon tetrachloride–light petroleum), m. p. 167° (Found: C, 33·6; H, 3·15%; equiv., 319); 2 : 4 : 6-trichlorophenetole (10·3 g.), b. p. 246—250° (Faust, *Annalen*, 1869, **149**, 152, gives b. p. 246°) (Found: C, 42·4; H, 3·0%), and 2 : 4 : 6-*trichlorophenoxymethylphosphonic acid* [1·8 g. from 2 g. of the half-ester; considerable frothing occurred in this reaction, and an excess of hydrochloric acid (50 ml.) was required because of the insolubility of the half ester], needles (from acetone–carbon tetrachloride), m. p. 217—218° (Found: C, 28·75; H, 2·1. $C_7H_6O_4Cl_3P$ requires C, 28·85; H, 2·1%). Reaction of sodium phenoxide (9·2 g.) and diethyl iodomethylphosphonate (9·2 g.) in a similar manner gave phenetole (3·7 g.), b. p. 170° (Pinette, *Annalen*, 1888, **243**, 35, gives b. p. 170·3°), and an acidic oil (9 g.); this was distilled *in vacuo* to give a neutral fraction (1·5 g.), b. p. 138°/2 mm. (Found: C, 50·2; H, 6·5. Calc. for $C_9H_{13}O_4P$: C, 50·0; H, 6·05%), and a residue (5·6 g.) which crystallised; this, *phenoxymethylphosphonic acid*, separated from acetone–carbon tetrachloride as plates, m. p. 139—141°, which retained a small amount of water of crystallisation after being dried *in vacuo* (Found: C, 43·75; H, 4·8. $C_7H_9O_4P,\frac{1}{4}H_2O$ requires C, 43·65; H, 4·95%); the same acid was also obtained by hydrolysis of either the acidic oil or the neutral compound with concentrated hydrochloric acid; an ethereal

solution of the acid with *n*-pentylamine gave the n-*pentylammonium salt hemihydrate* which separated from propan-2-ol as laths, m. p. 170° (decomp.) (Found: C, 55·05; H, 9·6; N, 7·75. $C_7H_9O_4P,2C_5H_{13}N,\frac{1}{2}H_2O$ requires C, 54·95; H, 9·75; N, 7·55%).

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THE UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA.

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The Sorption of Water Vapour by Active Carbon.

By M. M. DUBININ, E. D. ZAVERINA, and V. V. SERPINSKY.

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A detailed study has been made of sorption isotherms for water vapour on non-porous, heat-treated channel black of known specific area, and on a number of specimens of active carbon.

For channel black or active carbon the main rise of the sorption isotherms up to points where they bend corresponds to unimolecular adsorption. The region of multimolecular adsorption in a direct sorption process extends up to high relative pressures, approaching 0·95. Capillary condensation is insignificant for the specimens of active carbon studied.

Views being developed in this laboratory on the mechanism of adsorption of water vapour by carbon absorbents, and related to a hypothesis of the principal rôle played by hydrogen bonds in such adsorption, are expounded. The experimental results are shown to be in agreement with these views.

THE shape of the isotherm for the sorption of water vapour by active carbon differs markedly from that for sorption of organic vapours. Up to relative pressures of 0·4—0·5 (p/p_s, where p is the actual pressure of the vapour and p_s is the saturated vapour pressure), water vapour is adsorbed by active carbon only to a very small extent. At higher relative pressures a sharp rise occurs in the sorption and desorption branches of the isotherm which form a hysteresis loop typical for water vapour sorption (Dubinin and Zaverina, *Zhur. fiz. Khim.*, **1947**, **21**, 1373).

All workers, especially those of the American school, explain the sharp rise in these branches by a process of capillary condensation of the water vapour. On the basis of such views methods for calculating the distribution of the volume of pores in active carbon as a function of their radii have become common (Wiig and Inhola, *J. Amer. Chem. Soc.*, 1949, **71**, 561; Inhola and Wiig, *ibid.*, p. 2069). Work conducted jointly by the Sorption Processes Laboratory of the Institute for Physical Chemistry and the Adsorption Laboratory of the Moscow State University in the last two years has necessitated a substantial revision of these accepted views. Experimental investigations included a comparative study of the isotherms of the sorption and the desorption of water vapour by porous and non-porous carbon adsorbents whose surface could not have differed to any extent in chemical properties. The theoretical generalization expresses the views that have been crystallizing in the two laboratories mentioned above.

Experiments were made with non-porous channel blacks with spherical particles and a number of specimens of active carbon among which all types of pores were developed sufficiently. The adsorbents were heat-treated at 950°. Sorption scales employing the vacuum method (Dubinin and Zaverina, *Acta Physicochim. U.R.S.S.*, **1936**, **4**, 647) were used for obtaining sorption and desorption isotherms for benzene and water vapour at 20°.

Fig. 1 shows the isotherms for the sorption and desorption of benzene vapour by two types of heat-treated channel blacks: C-1, a powder, and C-2, briquetted without the use of binding agents. In the region of adsorption up to $p/p_s = 0·78$ the values for adsorption and desorption are well satisfied by one curve. The rise in the curves at higher p/p_s values

is mainly due to the capillary condensation of benzene vapours in the spaces formed by the touching particles of channel black.

Fig. 2 gives a linear representation of the experimental results for the adsorption of benzene vapour by powdered and by briquetted channel black at 20°, according to Brunauer, Emmett, and Teller's isotherm equation (*J. Amer. Chem. Soc.*, 1938, **60**, 309). The volume of gas needed to form an unbroken monolayer on the channel black calculated from the equation constants is $a_m = 0{\cdot}365$ mmole/g. Assuming the most plausible value

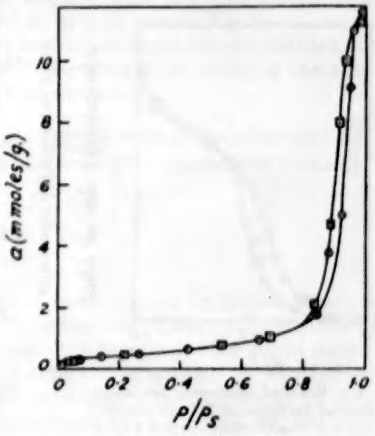


FIG. 1. *Isotherm for the sorption, ○, and desorption, □, of benzene vapour on channel black at 20°.*

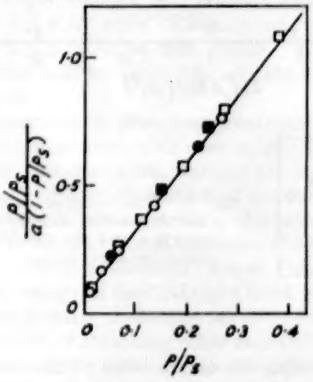


FIG. 2. *Isotherms for the adsorption of benzene vapour at 20° in linear form: ○, channel black powder; □, channel black briquettes; black symbols, desorption points.*

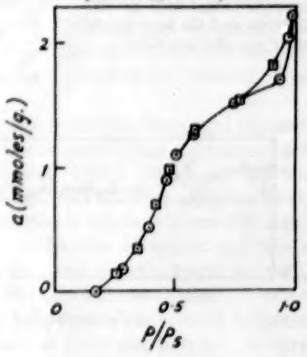


FIG. 3. *Isotherms for the sorption and desorption of water vapour on channel black at 20°: ○, adsorption; □, desorption.*

of the molecular area of benzene in a monolayer to be $\omega = 46{\cdot}5$ Å^2 (after Kiselev, Karnauhov, and Khrapova, *Doklady Akad. Nauk S.S.S.R.*, 1953, **92**, 361), we find that the specific area of the channel black will be $s = 103$ m.^{2}/g. Direct measurements using an electron microscope, carried out by Radushkevich and Lukjanovich, gave the figure $s = 98$ m.^{2}/g. Hence, the channel black studied may be considered a non-porous carbon adsorbent.

Fig. 3 shows the isotherms for the sorption and desorption of water vapour by channel black at 20°. At low equilibrium pressures there is but little adsorption of water vapour. In the medium range of relative pressures the adsorption is reversible and, as in the case of

active carbon, a sharp rise of the isotherm branch is observed. The change in the curve, at a relative pressure of 0·55, corresponds to an adsorption value of $a = 1{\cdot}20$ mmoles/g. As the maximum sorption value is approached, there is a rise in the isotherm again, a hysteresis loop being formed by the sorption and desorption branches in this range of relative pressures.

According to Harkins and Jura (*J. Amer. Chem. Soc.*, 1944, **66**, 1366) the molecular area in an unbroken monolayer of water is 14·8 Å². The specific area of channel black being 103 m.²/g., the filling of the monolayer corresponds to an adsorption value of $a_m = 1{\cdot}15$

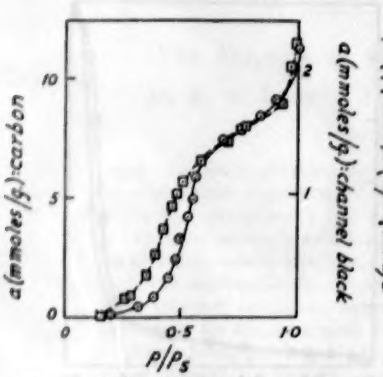


FIG. 4. *Reduced isotherms for water vapour sorption at 20° on channel black (□) and active carbon 1 (○).*

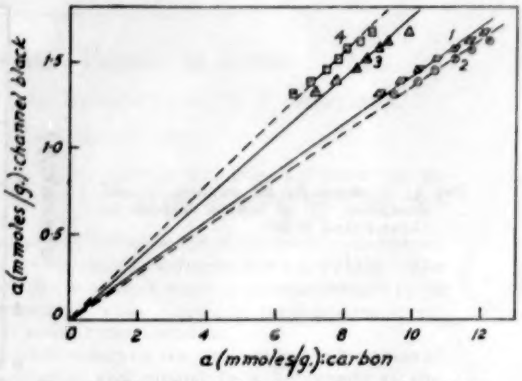
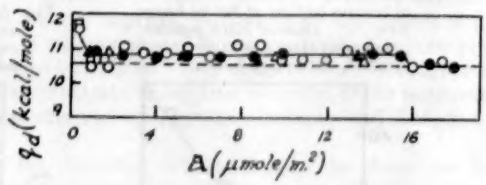


FIG. 5. *The relation of water vapour sorption values at 20° on channel black and active carbons 1 and 4 at similar equilibrium pressures.*

FIG. 6. *The relation between the differential heat of adsorption and the adsorption value for channel black.*



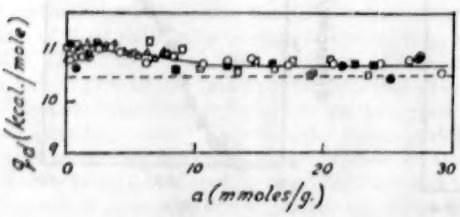


FIG. 7. *The relation between the differential heat of adsorption and the adsorption value for active carbon.*

mmoles/g. This figure coincides almost exactly with the termination of the main rise of the isotherm and its break at $a = 1{\cdot}20$ mmoles/g. Thus, for channel black on the average, only unimolecular adsorption is observed in the range of relative pressures up to 0·55.

Multimolecular adsorption at higher pressures is complicated in the vicinity of the saturation point by capillary condensation of water vapour in the spaces between the spherical particles of channel black in contact.

Fig. 4 shows, by way of illustration, the sorption branches of the isotherms for water vapour on channel black and active carbon 1, different scales being used for the *y*-axis. The regions of sharp rise are moved somewhat, owing to minor differences in the surface properties of active carbon and channel black. The points where the curves bend, both for soot and for active carbon at $p/p_s = 0{\cdot}55$, evidently correspond to the completion of the

formation of a continuous unimolecular adsorption layer. At this point, the properties of the surfaces of both channel black and carbon for all practical purposes become identical, and the adsorption isotherms shown coincide in the range of relative pressures from 0·55 to 0·95 in which adsorption is multimolecular.

The concurrence of the isotherms shown in the range of relative pressures mentioned points to their identity. The criterion for correspondence of the isotherms is a linear relation between the quantities of water adsorbed on channel black and on carbon at identical equilibrium pressures, it being necessary that the straight lines pass through the origin. This requirement is fulfilled for the carbons studied, as may be seen in Fig. 5.

The coefficients of affinity of the isotherms show how much larger the specific area of the carbons is than that of channel black. In Table 1 the calculated values of the affinity coefficients and the specific areas of the active carbons are listed.

TABLE 1. *Affinity coefficients of the isotherms and specific areas of the active carbons.*

Adsorbent	Affinity coefficient of the isotherms (K)	Specific area, s ($m.^2/g.$)
Channel black	1·00	103
Carbon 1	5·15	530
„ 2	5·75	590
„ 3	7·08	730
„ 4	7·42	765

Another characteristic feature of the adsorption of water vapour by channel black and active carbon is the closeness of the values of the differential heat of adsorption and the heat of condensation of water vapour in the volume phase over practically the entire region of fillings. The charts contain curves of the heat of differential adsorption for channel black (Fig. 6) and active carbon (Fig. 7), based on direct calorimetric measurements by Avgul, Dshigit, Kiselev, and Shtsherbakova (*Doklady Akad. Nauk S.S.S.R.*, 1953, **92**, 105). The heat of condensation level is indicated by a broken line.

According to the views held in our Laboratory the sharp rise of the adsorption branch of the isotherms for water vapour on carbon adsorbents is related to the formation of a condensed unimolecular adsorption layer, in which process the main rôle is played by the hydrogen bonds (Avgul, Dshigit, and Kiselev, *ibid.*, 1952, **86**, 95; Baring and Serpinsky, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1953, **6**, 957; Dubinin and Serpinsky, *Doklady Akad. Nauk S.S.S.R.*, 1954, **100**, No. 2). It is important that the nature of the surface of the adsorbent should be taken into account in considering a possible mechanism for sorption of water vapour.

In our experiments, after heat-treatment at 950°, the active carbons and channel black were brought into contact with atmospheric oxygen. Consequently, as a result of activated adsorption or chemisorption, surface oxides were formed which could not be destroyed during the preliminary evacuation of the carbons at 450°. It may be assumed that in the region of low equilibrium pressures the adsorption of water vapour is mainly due to the formation of hydrogen bonds between the adsorbed molecules of water and the surface oxides of the carbon adsorbents (Avgul, Dshigit, Kiselev, and Scherbakova, *loc. cit.*). The relatively low energy of the hydrogen bond results in low adsorption values.

The adsorbed water molecules serve as subsidiary adsorption centres of a special kind which are capable of attaching other molecules by means of hydrogen bonds. As a result of this, with increasing pressure, two-dimensional islands of the condensed phase appear on the carbon surface, formed by the water molecules retained by the hydrogen bonds. The probability that this process will take place will grow with increasing pressure, within certain limits, because of the growth of the number of adsorption centres. The islands merge when the pressure becomes sufficiently large, and a single condensed unimolecular layer is formed. The sharp rise of the isotherm in the range of medium relative pressures is, evidently, a result of this peculiar process of forming islands of two-dimensional liquid which continues until the islands merge.

There are two factors which it is essential to consider when dealing with the problem of the stability of these complexes of associated water molecules formed on the surface of carbon adsorbents. The first is the surface oxides which serve as primary adsorption

centres. The relatively weak adsorbent field, in this case resulting mainly from dispersion forces, is the second. Whereas in the gaseous phase the water molecules are not associated since the energy of thermal motion is large enough to disrupt any complexes which may be formed, yet in the surface layer, on the other hand, the field of the adsorbent stabilises any complexes which may be formed and they do not fall apart (Dubinin and Serpinsky, *loc. cit.*).

Further increase of relative pressure after a condensed unimolecular layer has been formed is accompanied by multimolecular adsorption of water vapour, which is complicated by a process of capillary condensation when there is a favourable porous structure of the active carbon. With those active carbon specimens which were studied, capillary condensation is possible only in the region lying beyond the main rise in the sorption isotherms, which corresponds to the formation of a condensed monolayer. That multimolecular adsorption or capillary condensation plays the main part in the sorption of water vapour at relative pressures exceeding 0·55, follows from the maximum values for sorption per square metre of surface of active carbon. In the case of capillary condensation, at a relative pressure of 1, the volume of the filled pores is the main factor determining the maximum sorption capacity. It is difficult to conceive that this volume should be proportional to the surface area of the adsorbent. On the other hand, if the main rôle is played by multimolecular adsorption, the difference between the absolute values for the maximum sorption capacity of various specimens of carbon must be very small. In Table 2, the results of the corresponding calculations made on the basis of the experimental data are given.

TABLE 2. *Maximum sorption capacities per unit of surface area of active carbons.*

Adsorbent	Specific area s (m.²/g.)	Maximum sorption capacity a_s (mmoles/g.)	$\bar{a}_s = a_s/s$ (mmoles/m.²)
Channel black	103	2·21	0·021
Carbon 1	530	11·3	0·021
,, 2	590	12·6	0·021
,, 3	730	14·9	0·020
,, 4	765	15·8	0·021

The practical identity of the maximum values for water-vapour sorption for non-porous soot and for the specimens of active carbons studied indicates that in the direct sorption process the region of multimolecular adsorption extends up to high relative pressures that approach unity. Capillary condensation can have played only a very small part in our sorption experiments.

In the light of the results which this study has produced, the region of relative pressures in which capillary condensation of water vapour in the pores of active carbon in the direct sorption process is possible, is shifted into the region of higher relative pressures. The main rise of the sorption branch of the isotherm is not due to capillary condensation, but is a result of the process of formation of a condensed unimolecular adsorption layer, *i.e.*, a stage which precedes capillary condensation. It should be noted that it is possible, as in the case of the carbon specimens studied, that given the proper porous structure of the active carbon, the completion of the formation of a condensed adsorption layer does not involve any noticeable bend in the sorption branch of the isotherm because of a superimposed process of capillary condensation.

The complexity of the sorption process for water vapour over the entire range of equilibrium relative pressures makes a simple approach to a quantitative analysis of the whole sorption branch of the isotherm rather unpromising. Registering the maximum for unimolecular adsorption is of no real interest in the case of active carbons because the volumes of the micropores are filled at maximum sorption. Consequently, we shall restrict ourselves to the region of unimolecular adsorption which, for active carbons, corresponds to adsorption values up to 10 mmole/g. (Dubinin and Serpinsky, *loc. cit.*). This region includes the beginning of the isotherm, the transition to the sharp rise of the sorption branch, and a substantial part of the rapidly rising curve, *i.e.*, all that is most characteristic for the sorption of water vapour.

Let a_0 be the number of primary adsorption centres, expressed in mmoles/g. If a

mmoles/g. is the adsorption at the relative pressure of $h = p/p_s$, then the condition for dynamic equilibrium of adsorption will be

$$k_2(a_0 + a)h = k_1 a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The left-hand expression is the probability of adsorption, which is proportional to the total number of primary and secondary adsorption centres, $a_0 + a$, and to the equilibrium pressure h. The probability of desorption on the right-hand side is proportional to the adsorption value a.

If c indicates the ratio of the rate constants k_2 and k_1, then according to (1) the equation of the adsorption isotherm, true only for the main region of unimolecular filling of the surface, will be

$$a = a_0 ch/(1 - ch) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

At relative pressures, for which $ch \ll 1$, the adsorption value is proportional to the pressure. In the vicinity of $h = 1/c$ a sharp rise of the isotherm branch occurs. In keeping with the assumptions made at the outset, equation (2) does not take the maximum of

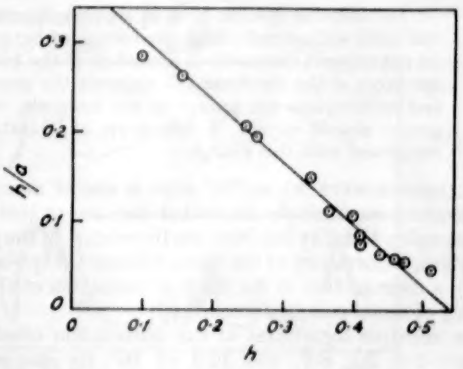


FIG. 8. *Adsorption isotherm for water vapour in linear form for carbon* B2 *over a range of adsorption from* 0·15 *to* 10 *mmoles/g.*

adsorption into account and is valid only for $h < 1/c$. In the linear form, the equation of the adsorption isotherm becomes

$$h/a = 1/a_0 c - h/a_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

An example is shown on Fig. 8, which gives a linear representation of the adsorption branch for water vapour on active carbon B2 with acid surface oxides at $a < 10$ mmoles/g. ($a_s = 26{\cdot}4$ mmoles/g.) according to experiments by E. D. Zaverina. The experimental points are generally well satisfied by a straight line. For the carbon B2, $a_0 = 1{\cdot}43$ mmoles/g. and $c = 1{\cdot}85$. The equation may be used up to $a = 9$ mmoles/g. Thus $a' \gg a$.

For a specimen of active carbon with a surface of the usual type, not containing any acid surface oxides, $a_0 = 0{\cdot}41$ mmole/g. and $c = 1{\cdot}77$. In the case of heat-treated channel black we obtained $a_0 = 0{\cdot}17$ mmole/g. and $c = 1{\cdot}78$. The values of the constants a_0 correspond to the content of chemically combined oxygen in the carbon adsorbents listed. The constants c are confined to a relatively narrow range which indicates that the heat of adsorption entering into the expression for the constant c does not vary substantially for the adsorbents studied. Consequently, in all these cases adsorption depends on forces of one and the same kind, which we believe to be the hydrogen bond. Hence, the values of the constants of the equation of the adsorption isotherm (2) are physically justified.

The value for the heat of condensation of water vapour λ in the volume phase depends mainly on the hydrogen bond. As was mentioned above, according to experiments by Avgul *et al.* (*loc. cit.*, 1953), the differential heat of adsorption q_d of water vapour on channel black and active carbons is close to the heat of condensation for water over the entire range of sorption values ($q_d \approx \lambda$). This is weighty evidence and additional proof that the forces

of interaction between the water molecules in the liquid phase and the forces of adsorption are of an identical physical nature. At the same time it indicates that the porous structure of carbon does not, to any considerable degree, influence the extent of adsorptional interaction, in contrast to the case where the dispersion forces are involved. The natural explanation of this fact is the chemical nature of adsorption interaction—the effect of the hydrogen bond.

LABORATORY OF SORPTION PROCESSES, INSTITUTE OF PHYSICAL CHEMISTRY,
ACADEMY OF SCIENCES OF THE U.S.S.R., MOSCOW. [*Received, December 3rd*, 1954.]

The Infrared Spectra of Ethylenediaminetetra-acetic Acid and its Di- and Tetra-sodium Salts.

By D. CHAPMAN.

[Reprint Order No. 6028.]

The infrared spectra of solid ethylenediaminetetra-acetic acid and its di- and tetra-sodium salts have been obtained between 650 and 3500 cm.$^{-1}$; they do not support the mode of ionisation of the acid previously suggested. The spectrum of the disodium salt suggests the presence of both carboxylic acid and carboxylate ion groups in the molecule, whereas only carboxylate ion groups should occur. A new mode of ionisation for the acid is suggested consistent with this evidence.

ETHYLENEDIAMINETETRA-ACETIC ACID is one of many polycarboxylic amino-acids which are becoming increasingly important because of their stable complexes with metal ions. Since complex stability has been partly related to the proton affinity of these acids (Martell and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, New York, 1952, p. 159), a clear picture of the mode of ionisation of the acids could lead to a better understanding of metal complex formation.

The negative logarithms of the dissociation constants of ethylenediaminetetra-acetic acid are 2·0, 2·7, 6·2, and 10·3 at 20° for successive protons (Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798). This sequence of acid strengths was explained by supposing that a double betaine structure of the acid is formed. Thus, the first two, strongly acid, protons ionise from the carboxyl groups, and the third, of intermediate character, and the fourth, only feebly acidic, ionise from the respective nitrogen atoms. In order to explain the remarkable intermediate value of pK_3 the existence of a hydrogen bridge was invoked joining the two nitrogen atoms, the difference between pK_3 and pK_4 being attributed to the energy produced on formation of the bridge (cf., however, Carini and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4814).

If this mode of ionisation is correct, there should be no evidence of carboxyl groups in the infrared spectrum of the disodium salt and only carboxylate-ion group frequencies should appear. In order to confirm this, the infrared spectrum of this salt has been studied. To aid interpretation, the spectra of the acid and its tetrasodium salts were also recorded.

Experimental.—The sample of ethylenediaminetetra-acetic acid used was an analytical reagent (Messrs. Hopkin and Williams). The disodium salt was a B.D.H. laboratory reagent recrystallised. The tetrasodium salt was obtained by adding the requisite amount of sodium hydroxide to a solution of the disodium salt in water, and precipitation with alcohol.

Apparatus and Technique.—A Grubb-Parsons double-beam spectrometer with rock-salt prism was used. The crystalline specimens were dispersed in Nujol between rock-salt plates. The spectra of the di- and tetra-sodium salt were obtained both before and after heating them over phosphoric oxide at 110°. Spectra were obtained from 3500 to 650 cm.$^{-1}$. The results are given in the figure and the following table (where ν is in cm.$^{-1}$, w = weak, and vw = very weak).

Acid: 2933 (Nujol), 2659 (associated OH), 1698 (C=O), 1460 (Nujol), 1414 (CH_2·CO_2H), 1370 (Nujol), 1345, 1318 (CO_2H), 1259 (vw), 1237 (vw), 1214 (w), 1135 (w), 1091 (w), 1054, 1043, 1006, 983, 967, 870, 778 (broad region), 714.

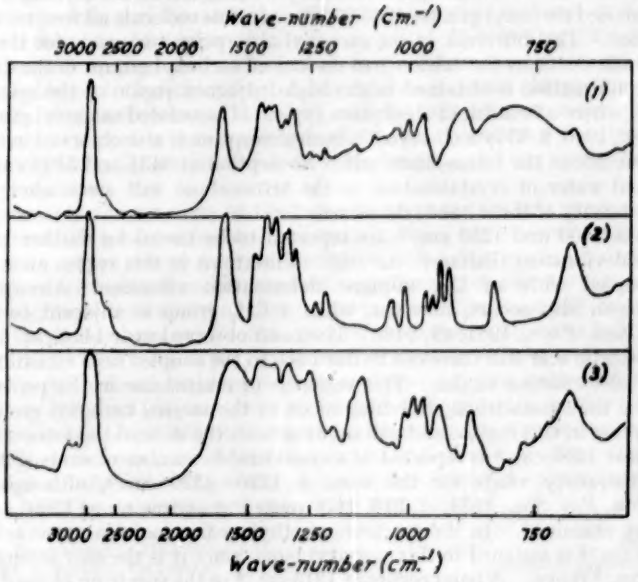
Disodium salt: **2933** (Nujol), **2713**, **2596** (assoc. OH), **1668** (C=O), **1637** ν_a(O–C–O), **1460** (Nujol), **1398**, **1370** (Nujol), **1327**, **1315** (CO_2H), **1286**, **1223**, **1195**, **1056**, **1020**, **959**, **937**, **919**, **900**, **811**, **712** *b*( ) mode.

Tetrasodium salt: **3434**, **3197** (H_2O of crystn.), **2933** (Nujol), **1597** ν_a(O–C–O), **1443** (Nujol), **1372** (Nujol), **1325**, **1251**, **1185**, **1137**, **1115**, **1012**, **988**, **958**, **914**, **880** (w), **849**, **786** (w), **762** (w), **734** (w), **709** *b*( ) mode.

Discussion

The infrared spectra of a great number of simple amino-acids have been obtained, and the positions of the absorption bands of the ionised carboxyl group fairly well established.

Infra-red spectra of: (1) *ethylenediaminetetra-acetic acid*; (2) *disodium dihydrogen ethylenediaminetetra-acetate*; (3) *tetrasodium ethylenediaminetetra-acetate.*



Thompson, Nicholson, and Short (*Discuss. Faraday Soc.*, 1950, **9**, 222) suggest the narrow range of 1600—1590 cm.$^{-1}$, and Fuson, Josien, and Powell (*J. Amer. Chem. Soc.*, 1952, **74**, 1) suggest the range 1600—1560 cm.$^{-1}$ for this band. In the case of dicarboxylic amino-acids both the ionic and the non-ionic carbonyl bands are reported to appear (Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 207).

In view of these data it is noteworthy that ethylenediaminetetra-acetic acid does not have an ionised carboxyl group as would be expected if the molecule had a betaine structure. The frequency of the carboxyl band in the acid is at 1698 cm.$^{-1}$, showing the carboxyl groups to be quite normal, and presumably associated by hydrogen bonding. That the acid does not possess a typical betaine structure in the solid state suggests that the tendency of the molecule to form a zwitter-ion is less than in simple amino-acids such as glycine or alanine, although an alternative explanation might be that there is preferential hydrogen bonding for this molecule in the crystal.

The spectrum of disodium dihydrogen ethylenediaminetetra-acetate shows a number of

significant features (see figure). On Schwarzenbach and Ackermann's mode of ionisation, the salt should have four carboxylate groups and no un-ionised carboxyl groups. There should therefore be one strong band between **1560** and **1600** cm.$^{-1}$ due to the asymmetric stretching frequency ν_a(O—C—O) of the ionised carboxyl group. The spectrum of the hydrated disodium salt shows two bands at **1686** and **1637** cm.$^{-1}$ and two strong OH stretching bands in the **3300**-cm.$^{-1}$ region. After heating of the compound over phosphoric oxide *in vacuo* the **3300** and the **1686**-cm.$^{-1}$ band vanish, showing these bands to be due to water of crystallisation. The remainder of the spectrum is unaltered. A band at **1668** cm.$^{-1}$ as well as the **1637**-cm.$^{-1}$ band can now be clearly observed, however. The frequency of the **1668**-cm.$^{-1}$ band is rather high to be assigned to an ionised carboxyl asymmetric stretching frequency, and even the **1637**-cm.$^{-1}$ band is a little higher in frequency than the range **1600—1560** cm.$^{-1}$ (Fuson, Josien, and Powell, *loc. cit.*) given for the normal ionised carboxyl group in amino-acids. The high-frequency **1668**-cm.$^{-1}$ band and the small shift in frequency of this band from that observed in the acid (**1698** cm.$^{-1}$) are therefore taken to indicate the presence of un-ionised carboxyl groups in the disodium salt.

The spectrum of the tetrasodium salt shows a strong broad band with maximum absorption at **1590** cm.$^{-1}$. This band can clearly be assigned to the asymmetric stretching mode of the ionised carboxyl group ν_a(O—C—O). In this molecule all four carboxyl groups must be ionised. The difference in the carbonyl absorption frequency for the di- and the tetra-sodium salt confirms the existence of un-ionised carboxyl groups in the disodium salt.

Further confirmation is obtained in the high-frequency region of the spectrum of the disodium salt, where a breadth of absorption typical of associated carboxyl groups (Davies, *J. Chem. Phys.*, **1940**, **8**, 577) is observed. Such absorption is also observed in the spectrum of the acid but not in the tetrasodium salt. Absorption at **3434** and **3197** cm.$^{-1}$ is clearly due to residual water of crystallisation in the tetrasodium salt since after it has been heated, the intensity of these bands decreases.

The regions **1400** and **1250** cm.$^{-1}$ are reported to be useful for further characteristic carboxylic acid vibration (Bellamy, *loc. cit.*). Vibrations in this region arise from a C–O vibration coupled with an OH in-plane deformation vibration. Absorption in the 1400-cm.$^{-1}$ region also occurs, however, when a CH_2 group is adjacent to a CO group (Francis, *J. Chem. Phys.*, 1951, **19**, 942). The band observed near **1414** cm.$^{-1}$ in ethylenediaminetetra-acetic acid will therefore be due both to the coupled C–O vibration and to the CH_2-modified deformation modes. This region is of limited use in the present problem, however, since the symmetrical stretching mode of the ionised carboxyl group also gives rise to absorption in this region, and will occur in both the di- and the tetra-sodium salt.

A band near **1250** cm.$^{-1}$ is reported in a considerable number of acids (Flett, *J.*, 1951, 962). The frequency range for the band is **1210—1320** cm.$^{-1}$, although Hadzi and Sheppard (*Proc. Roy. Soc.*, **1953**, *A*, **216**, 247) quote the narrow range **1300** ± **15** cm.$^{-1}$ for the acids they examined. In the spectrum of ethylenediaminetetra-acetic acid the strong band at **1318** cm.$^{-1}$ is assigned to this carboxyl band, since it is the only strong band in the **1210—1320** cm.$^{-1}$ range. A band occurs at **1315** cm.$^{-1}$ in the spectrum of the disodium salt.

Since the disodium salt contains both carboxyl and carboxylate ion structures, and the acid itself is un-ionised, it might be expected that the spectrum of the disodium salt would be more or less a superposition of the spectra of the acid and the tetrasodium salt. The limitation to this is set by the intramolecular interaction between the carboxyl and carboxylate groups. To a certain extent this simple picture holds, although the difference (**23** cm.$^{-1}$) between the ν(C=O) and ν_a(O—C—O) frequencies for the disodium salt is rather small :

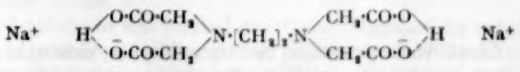
Acid	**1698**	—	**1318**	—
4Na	—	**1597**	—	**709**
2Na	**1668**	**1637**	**1315**	**712**
Assignment	ν(C=O)	ν_a(O—C—O)	2*b* (?)	*b*

In a similar study of potassium hydrogen bisphenylacetate (Davies and Thomas, *J.*, 1951, 2858) a much greater νC=O − ν_a(O—C—O) difference was observed and " super-

position " was in general better. However, owing to displacements, etc., which can occur in the solid state, the simple picture seems entirely adequate.

Since the disodium salt does not possess a double betaine structure, a new mode of ionisation consistent with this must be found. Flett (*loc. cit.*) has shown that, of nine acids with carbonyl frequencies below 1680 cm.$^{-1}$, seven formed internal hydrogen bonds. Since the high-frequency carbonyl band in the disodium salt is at 1668 cm.$^{-1}$, it seems reasonable to suppose that the two remaining protons in the disodium salt are each linked between a carboxyl and a carboxylate ion. An analogous situation exists in maleic acid where, in the ion formed by half-dissociation, the carboxyl and carboxylate group attract each other, being linked by a hydrogen bond. This stabilises the ion (cf. Speakman, *J.*, 1949, 3357).

The mode of ionisation proposed is therefore the following. The first and the second proton are removed from opposite ends of the molecule, which then acts to a first approximation as two dibasic acids. The disodium salt will then have the structure:



The third proton will be removed from between the carboxyl–carboxylate link, and pK_3 will therefore be higher than pK_1 or pK_2. At this stage the fourth proton will tend to migrate to the nearby nitrogen atom, since now the zwitter-ion structure will be more probable and the possibility of having two positive charges on neighbouring nitrogen atoms does not occur. Thus pK_4 will be high, corresponding to the energy required to remove a proton from a nitrogen atom. In this manner the almost equal acid strength for pK_1 and pK_2, the intermediate value for pK_3, and the high value for pK_4 are satisfactorily explained.

It is presumably the nearness of the two nitrogen atoms which prevents the double-betaine structure being formed in the disodium salt, owing to the resultant repulsion which would arise if a positive charge were to develop on each nitrogen atom; and so it is to be expected that, in the higher homologues of ethylenediaminetetra-acetic acid, as the number of methylene groups between the nitrogen atoms increases, so will the tendency for formation of the double-betaine structure, and for the nitrogen atoms to hold the third and the fourth proton. The value of pK_3 will therefore increase in these higher homologues up to that of pK_4, the molecule tending more to act like (say) two methyliminodiacetic acid molecules where pK_1 and pK_2 are given as 2·1 and 9·65 respectively (Martell and Calvin, *loc. cit.*). This is consistent with the experimental values for the ionisation constants of these homologues (Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1948, **31**, 1029). The experimental values show that the pK_3 increases from 6·6 in ethylenediaminetetra-acetic acid to 9·5 in pentamethylenediaminetetra-acetic acid.

RESEARCH DEPARTMENT, UNILEVER LTD.,
PORT SUNLIGHT, CHESHIRE.

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Oenanthotoxin and Cicutoxin. Part II. The Synthesis of (±)-Cicutoxin and of Oenanthetol.*

By (Miss) B. E. Hill, B. Lythgoe, S. Mirvish, and S. Trippett.

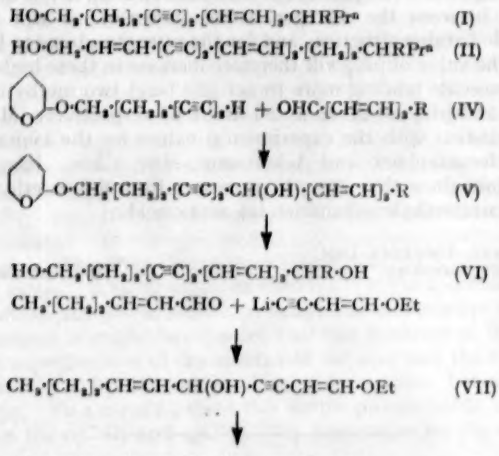
[Reprint Order No. 6099.]

The structure of cicutoxin as (−)-heptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyne-1 : 14-diol is confirmed by synthesis of the (±)-isomer from a protected hepta-4 : 6-diyn-1-ol and deca-2 : 4 : 6-trienal. The natural and the synthetic compound have been oxidised to the same 1-hydroxyheptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyn-14-one.

Oenanthetol (heptadeca-*trans*-2 : 8 : 10-triene-4 : 6-diyn-1-ol), from *Oenanthe crocata*, has been synthesised by dehydrating heptadeca-2 : 8-diene-4 : 6-diyne-1 : 10-diol.

The water hemlock, *Cicuta virosa*, contains two triene-diynes, cicutoxin (I; R = OH) and cicutol, and the hemlock water dropwort, *Oenanthe crocata*, contains three ene-diyne-dienes, oenanthotoxin (II; R = OH), oenanthetol, and oenanthetone (Anet, Lythgoe, Silk, and Trippett, Part I *). Although complete degradative evidence was obtained for the structures allotted to the two toxins, those of cicutol and oenanthetol were assumed to be (I; R = H) and (II; R = H) respectively by analogy; the orientations of the unsaturated systems within their molecules (as distinct from their positions) were not directly determined. Synthetic work has been undertaken in order to confirm the postulated structures and this paper records syntheses of representatives of both groups of compounds, namely, (±)-cicutoxin and oenanthetol.

Cicutoxin appeared to be the most readily amenable of the five naturally occurring compounds to synthesis, since it contains a secondary allylic hydroxyl group and should be accessible by reaction of a Grignard derivative of a suitably protected hepta-4 : 6-diyn-1-ol



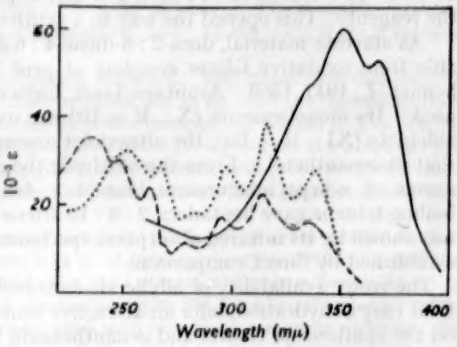
(*e.g.*, III) and deca-2:4:6-trienal (IV; R = Prⁿ). The first of these components was readily obtained by reaction of 1-bromo-3-2′-tetrahydropyranyloxypropane with monosodiodiacetylene in liquid ammonia. As a means of testing the projected synthesis the magnesium bromide derivative from (III) was treated with octatrienal to give the alcohol (V; R = Me). Treatment with acid removed the protecting tetrahydropyranyl residue and

* Part I, *J.*, 1953, 309.

caused anionotropic rearrangement to the (±)-diol (VI; R = Me); this diol differs from cicutoxin only in its stereochemistry at $C_{(14)}$ and in having a methyl instead of a *n*-propyl group. Its infrared absorption spectrum showed that, as expected from its mode of synthesis, it had the all-*trans*-structure, and its ultraviolet absorption spectrum was very similar to that of cicutoxin. It absorbed 7 mols. of hydrogen in the presence of palladium, giving (±)-pentadecane-1 : 14-diol.

For the preparation of deca-2 : 4 : 6-trienal (IV; R = Pr^n) hex-2-en-1-al was chosen as the starting material. It was obtained by reducing hex-2-enoic acid with lithium aluminium hydride to hex-2-en-1-ol which was oxidised with manganese dioxide to hex-2-enal. Reaction of the aldehyde with the lithium derivative of ethoxyvinylacetylene (cf. Inhoffen, Bohlmann, and Rummert, *Annalen*, 1950, **569**, 226) gave crude 1-ethoxydeca-1 : 6-dien-3-yn-5-ol (VII) which, after semihydrogenation with Lindlar's catalyst (*Helv. Chim. Acta*, 1952, **35**, 446) and subsequent treatment with acid, gave the trienal (IV; R = Pr^n), isolated as its semicarbazone.

The regenerated aldehyde was treated exactly as described for octatrienal and the final product purified chromatographically, giving (±)-cicutoxin (VI; R = Pr^n; *i.e.*, I; R = OH) with light absorption almost identical with that of natural (−)-cicutoxin. It had, as



Light absorption of (——) *1-hydroxyheptadeca-8 : 10 : 12-triene-4 : 6-diyn-14-one* (*in* CCl_4), (– – – –) *10-benzoyloxydeca-2 : 8-diene-4 : 6-diynal* (*in* EtOH), *and* (. . . .) *oenanthetol* (*in* EtOH).

expected from the mode of synthesis, an all-*trans*-structure, and the infrared absorption spectra of the natural and the synthetic material, compared in chloroform solutions, showed no discrepancies. That the two samples were identical in all save the stereochemistry at $C_{(14)}$ was shown chemically by oxidation with manganese dioxide to the same crystalline 1-hydroxyheptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyn-14-one, the light absorption of which is shown in the Figure. Dr. G. A. Mogey of the Department of Pharmacology, to whom we express our warm appreciation, tested the effect of the natural and the synthetic material on mice. The synthetic material was considerably more toxic, pointing to a considerably greater potency of the (+)-component than the natural isomer. This is of special interest in connection with our observation that natural oenanthotoxin, which has the (+)-configuration, is more toxic to mice than (−)-cicutoxin.

Attention was then turned to oenanthetol (II; R = H), whose synthesis was expected to present more problems than that of cicutoxin. Trideca-*trans*-3 : 5 : 11-triene-7 : 9-diyn-2-ol, which has the same unsaturated system as oenanthetol, was prepared (Part I, *loc. cit.*) by reaction of a Grignard derivative of hept-2-ene-4 : 6-diyne with sorbaldehyde followed by anionotropic rearrangement of the resulting alcohol, and, theoretically, the alcohol (VIII; R = $C_6H_{13}^n$; *n* = 1), accessible from trideca-5 : 7-diene-1 : 3-diyne and acraldehyde, should give oenanthetol by similar rearrangement. However, when such rearrangements displace only one ethylenic link in a system devoid of activating alkyl groups, they are known to proceed only with difficulty (Heilbron *et al.*, *J.*, 1945, 77, 84). The alcohol (VIII; R = Me; *n* = 1) should offer a suitable test substance; but the product from bromomagnesiohept-2-ene-4 : 6-diyne and acraldehyde could not be rearranged to an ene-diyn-ene, and this type of approach was abandoned.

An alternative appeared to lie in an oxidative coupling of the readily accessible pent-2-en-4-yn-1-ol with a dien-yne (IX). Such dien-ynes have not so far been prepared, but Eglinton and Whiting (*J.*, 1950, 3650) obtained pent-2-en-4-yne by the action of potassium hydroxide on the toluene-*p*-sulphonate of pent-4-yn-2-ol. Attempts to extend this method to hept-4-en-1-yn-3-ol gave discouraging results, nor could this alcohol be dehydrated directly by toluene-*p*-sulphonic acid without extensive destruction of the product. It seems likely, from results presented below, that this lability is caused by the terminal ethynyl group.

Search for methods of preparing dien-ynes such as (IX) was deferred since in the meantime it was observed that cicutoxin was readily dehydrated by toluene-*p*-sulphonic acid in

(VIII) $CH_2{=}CH{\cdot}CH(OH){\cdot}[C{\equiv}C]_2{\cdot}[CH{=}CH]_n{\cdot}R$ $\qquad$ $HC{\equiv}C{\cdot}[CH{=}CH]_2{\cdot}C_6H_{13}{}^n$ (IX)

(X) $RO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH \longrightarrow RO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CHO$ (XI) $\longrightarrow$

(XII) $HO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}C_6H_{13}{}^n \longrightarrow$ (II; R = H)

boiling benzene to give a product which, from its light absorption, was clearly heptadeca-4 : 6 : 8 : 10-tetraene-12 : 14-diyn-1-ol and appeared to be stable towards further action of the reagent. This opened the way to a synthesis of oenanthetol from the diol (XII).

As starting material, deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (X; R = H), readily available from oxidative Glaser coupling of pent-2-en-4-yn-1-ol (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586; Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998) was used. Its monobenzoate (X; R = Bz) was oxidised with manganese dioxide to the semi-aldehyde (XI; R = Bz), the ultraviolet absorption curve of which (see Figure) resembled that of oenanthetol. From the aldehyde the diol (XII) was obtained by reaction with an excess of *n*-heptylmagnesium bromide; dehydration with toluene-*p*-sulphonic acid in boiling toluene gave heptadeca-2 : 8 : 10-triene-4 : 6-dien-1-ol, whose all-*trans*-configuration was shown by its infrared absorption spectrum. Its identity with natural oenanthetol was established by direct comparison.

The ready availability of allylic alcohols such as (I; R = OH) and (XII), together with their easy dehydration, offer an attractive route to a variety of polyen-ynes. Experiments on the synthesis of cicutol and oenanthotoxin by this route are in progress.

Experimental

Operations with unsaturated compounds were carried out at low temperature under oxygen-free nitrogen. Light petroleum refers to the fraction, b. p. 40—60°. M. p.s are corrected.

1-Bromo-3-2′-tetrahydropyranyloxypropane.—2 : 3-Dihydropyran (28 g.) and trimethylene bromohydrin (42 g.) were mixed and, after the initial period when heat was evolved, were kept for 2 hr. at 20°, then diluted with ether (200 c.c.), and the solution was washed with aqueous sodium carbonate and then with water. Removal of the ether and distillation of the residue gave the *product* (62 g.) as a colourless liquid, b. p. 82—84°/0·3 mm. (Found: C, 43·1; H, 7·0. $C_8H_{15}O_2Br$ requires C, 43·1; H, 6·7%).

7-2′-Tetrahydropyranyloxyhepta-1 : 3-diyne.—To a solution of monosodiodiacetylene (Armitage, Jones, and Whiting, *J.*, 1952, 1993) prepared from 1 : 4-dichlorobut-2-yne (27 g.), ether (25 c.c.), and sodium (15·2 g.) in liquid ammonia (700 c.c.), the above bromo-compound (44·6 g.) in ether (25 c.c.) was added with stirring at —33°. Stirring was continued for 3 hr., then ether (300 c.c.) was added and the ammonia allowed to evaporate overnight in a current of nitrogen. The residue was extracted with ether (3 × 200 c.c.), and the solution washed with water, dried, and evaporated. Fractional distillation gave the *diyne* (10·2 g.) as an oil, b. p. (bath-temp.) 80—82°/10^{-4} mm., n_D^{20} 1·5010 (Found: 73·3; H, 8·6. $C_{15}H_{16}O_2$ requires C, 75·0; H, 8·3%). Light absorption in EtOH: max. at 226, 237, and 250·5 mμ (ε 350, 370, and 238).

Pentadeca-trans-8 : 10 : 12-triene-4 : 6-diyne-1 : 14-diol.—A solution of ethylmagnesium bromide, prepared from magnesium (1·41 g.), ethyl bromide (6·3 g.), and ether (100 c.c.), was stirred at 20° whilst the foregoing diyne (10·2 g.) in benzene (150 c.c.) was added. The mixture was stirred at 30° for 3 hr., then cooled to 0°, diluted with ether (100 c.c.), and treated dropwise with octatrienal (7·1 g.) in benzene (150 c.c.). Stirring was continued for a further 4 hr., and saturated aqueous ammonium chloride (200 c.c.) was added, the aqueous phase extracted with ether

(3 × 100 c.c.), and the combined benzene and ether phases were washed, dried, and evaporated. The crude product (20 g.) was shaken at 20° for 14 hr. with dioxan (120 c.c.), sulphuric acid (2·5 g.), and water (10 c.c.), the heterogeneous mixture diluted with ether (200 c.c.) and water (400 c.c.), and the ethereal layer dried and evaporated. Chromatography on morin–aluminium oxide as described for cicutoxin concentrates in Part I (*loc. cit.*) gave a red oily fraction (2·6 g.; purity 50%) containing the required diol, which was again chromatographed to give a fraction (900 mg.; purity 80%) which crystallised. Recrystallisation from benzene and finally from ether–light petroleum gave the (±)-*diol* as yellow crystals, m. p. 86° (Found: C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). Light absorption in EtOH: max. at 242, 251, 316·5, and 335·5 mμ, inflexion at 303 mμ ($10^{-3}\varepsilon$ 13·0, 21·5, 60·0, 59·7, and 35·0). The infrared spectrum (Nujol) showed *inter al.* bands at 3195 (s), 2208 (w), 2123 (w), 1600 (m), and 996 (v.s.) cm.$^{-1}$. Hydrogenation with palladium–charcoal (7·2 mols. of hydrogen) gave *pentadecane*-1 : 14-*diol* as crystals (from ether–light petroleum), m. p. 66° (Found: C, 72·6; H, 13·1. $C_{15}H_{32}O_2$ requires C, 73·6; H, 13·2%).

Hex-2-en-1-ol.—To a stirred solution of lithium aluminium hydride (16 g.) in ether (1 l.) hex-2-enoic acid (60 g.) in ether (500 c.c.) was added at a rate sufficient to maintain reflux of the ether, after which stirring was continued at room temperature for 2 hr. After addition of ethyl acetate excess of a concentrated aqueous solution of tartaric acid was added, and the ethereal layer was washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated. Distillation of the residue gave hex-2-en-1-ol (27·6 g.), b. p. 39°/0·15 mm. The *α-naphthylurethane* formed crystals, m. p. 73°, from light petroleum (Found: C, 75·7; H, 6·9. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

Hex-2-enal.—Hex-2-en-1-ol (27 g.), light petroleum (1500 c.c.), and manganese dioxide (270 g.) (Attenburrow *et al.*, *J.*, 1952, 1094) were shaken together for 16 hr., and the filtered solution was shaken for 2 hr. with excess of an alcoholic solution of semicarbazide acetate. The precipitated hex-2-enal semicarbazone (21 g.) had m. p. 175—176°. To regenerate the aldehyde the semicarbazone (58 g.) was heated with aqueous pyruvic acid in acetic acid (500 c.c.) for 15 min., the solution diluted with water, and the hexenal (35 g.) isolated with light petroleum and used directly for the next step.

1-*Ethoxydeca*-1 : 6-*dien*-3-*yn*-5-*ol.*—Ethoxyvinylacetylene (39·7 g.) in ether (250 c.c.) was treated with a solution of phenyl-lithium (from 5·74 g. of lithium) in ether (250 c.c.), and the solution heated under reflux for 45 min., cooled, and then stirred whilst hex-2-enal (35 g.) in light petroleum (200 c.c.) was added. Stirring was continued at 20° for 4 hr., then under reflux for 1 hr., then the mixture was cooled and decomposed with aqueous ammonium chloride, and the ethereal layer washed, dried, and evaporated. A solution of the residue in benzene was passed through a column of aluminium oxide; diphenyl was separated in the effluent. Elution with benzene–methanol (100 : 1) gave the crude *dienynol* which was purified by distillation, giving material (33·5 g.), b. p. 101—107°/0·2 mm. (Found: C, 74·4; H, 8·9. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

Deca-2 : 4 : 6-*trienal.*—The above dienynol (33·5 g.) was hydrogenated at 20° in ethanol in presence of Lindlar's catalyst (50 mg.; *loc. cit.*). After 5 hr. 3·92 l. of hydrogen (0·95 mol.) had been absorbed, the catalyst was removed, and the filtrate treated with alcohol (50 c.c.) and 20% aqueous sulphuric acid (10 c.c.) and kept overnight at 20°. Dilution with water and extraction with light petroleum gave the crude aldehyde from which *deca*-2 : 4 : 6-*trienal semicarbazone* (26·8 g.) was obtained as plates, m. p. 215° (decomp.), from 2-methoxyethanol (Found: N, 20·2. $C_{11}H_{17}ON_3$ requires N, 20·3%). Light absorption in alcohol: max. at 308, 321, and 337 mμ ($10^{-3}\varepsilon$ 41, 58, and 55). The infrared absorption spectrum showed *inter al.* bands at 1667 (s), 1592 (s), and 997 (s) cm.$^{-1}$. The aldehyde (yield 55%) regenerated by pyruvic acid treatment of the semicarbazone was sufficiently pure for use in the next step.

(±)-*Cicutoxin.*—The magnesium bromide derivative from 7-2′-tetrahydropyranyloxyhepta-1 : 3-diyne was prepared as described above from the diyne (7·0 g.) in ether (450 c.c.) and benzene (450 c.c.), and the mixture was cooled to 0° and stirred during the addition (1 hr.) of deca-2 : 4 : 6-trienal (6 g.) in benzene (100 c.c.). Stirring was continued at 0° for a further 4 hr., the mixture was finally decomposed with saturated aqueous ammonium chloride, and the product (12 g.) isolated in the usual way. Its solution in acetone (120 c.c.) containing concentrated sulphuric acid (2·5 g.) and water (10 c.c.) was kept at 20° for 18 hr., then diluted with water (400 c.c.), and the red oily product (13 g.) isolated with ether. Chromatography on morin–aluminium oxide (Part I, *loc. cit.*) gave a crude oily cicutoxin fraction (5·65 g.) estimated spectrometrically to contain 1·32 g. of cicutoxin. This was again chromatographed, giving as the purest fraction material (625 mg.; purity 50%) which crystallised at 0°. Recrystallisation of the crude

crystalline material from benzene and finally from ether–light petroleum gave (±)-*cicutoxin* (50 mg.) as colourless crystals, m. p. 67° (Found: C, 79·1; H, 8·7. $C_{17}H_{22}O_3$ requires C, 79·0; H, 8·6%). Light absorption in alcohol: max. at 242, 252, 318·5, and 335·5 mμ, inflection at 303 mμ ($10^{-3}\varepsilon$ 14·6, 21·6, 50·6, 60·3, and 37·0). The infrared absorption spectra of (±)-cicutoxin and natural (−)-cicutoxin measured in 10% solutions in chloroform were identical. In alcohol with palladium–charcoal (±)-cicutoxin absorbed 7·2 mols. of hydrogen.

1-Hydroxyheptadeca-trans-8 : 10 : 12-*triene*-4 : 6-*diyn*-14-one.—(−)-Cicutoxin (60 mg.), acetone (50 c.c.), and manganese dioxide (1·5 g.) were shaken together for 2 hr. and the solution was filtered and evaporated. The product crystallised from ether–light petroleum, giving *1-hydroxyheptadeca*-trans-8 : 10 : 12-*triene*-4 : 6-*diyn*-14-*one*, m. p. 84° (Found: C, 79·7; H, 8·3. $C_{17}H_{20}O_3$ requires C, 79·6; H, 7·8%). Light absorption in carbon tetrachloride: max. at 351 and 367 mμ, inflexion at 334 mμ ($10^{-3}\varepsilon$ 53·5, 60·5, and 46·5). The infrared absorption spectrum (Nujol) showed bands *inter al.* at 3145 (w), 2237 (m), 1681 (s), 1603 (s), and 1002 (s) cm.$^{-1}$.

Material identical in all respects was obtained by similar treatment of (±)-cicutoxin.

Dehydration of (±)-Cicutoxin.—A solution of the toxin (2 mg.) in benzene (110 c.c.) containing toluene-*p*-sulphonic acid (50 mg.) was boiled and aliquot portions of 1 c.c. were withdrawn for spectroscopic examination at intervals of 2½, 5, and 7½ min. In the first portion the absorption bands of cicutoxin had disappeared completely and new bands with max. (alcohol) at 255, 331, 347, and 367 mμ ($10^{-3}\varepsilon$ 55, 49, 73, and 75) had appeared. No further change was observed in the samples removed after 5 and 7½ min.

Deca-2 : 8-*diene*-4 : 6-*diyne*-1 : 10-*diol Monobenzoate.*—To a cooled and stirred solution of deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (45 g.) in pyridine (90 c.c.), benzoyl chloride (39 g.) in pyridine (45 c.c.) was added dropwise (3 hr.), and the mixture was kept overnight and then decomposed with ice and 20% sulphuric acid. Addition of ether precipitated some dibenzoate (m. p. 96°) which was removed. The ethereal solution was washed repeatedly with ice-cold 15% sulphuric acid and then dried, and kept at −40°, then more dibenzoate separated and was removed. Evaporation of the filtrate gave an oil which was treated with benzene whereupon unchanged diol, m. p. 154—155°, remained undissolved and was removed. The benzene solution was passed through a column of neutral alumina, development with benzene giving in the first portion of the effluent more dibenzoate. This was followed by monobenzoate, elution of which was completed by benzene–methanol (100 : 1). Finally, elution with methanol gave more unchanged diol. Crystallisation of the middle fraction from benzene–light petroleum gave the *monobenzoate* (22 g.), m. p. 65—65·5° (Found: C, 76·7; H, 5·3. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). Diol (6 g.) and its dibenzoate (15·2 g.) were obtained by recrystallisation of the appropriate fractions.

10-*Benzoyloxydeca*-2 : 8-*triene*-4 : 6-*diynal.*—The above monobenzoate (1·75 g.) was oxidised in the usual way with manganese dioxide (17·5 g.) in acetone (175 c.c.) for 4½ hr. and gave the required *aldehyde* as pale yellow crystals (from ether at −20°), m. p. 91—91·5° (Found: C, 77·0; H, 4·8. $C_{17}H_{12}O_3$ requires C, 77·3; H, 4·5%). Light absorption in alcohol: max. at 235, 248, 262, 278, 295, 314, and 335·5 mμ ($10^{-3}\varepsilon$ 35·0, 30·3, 24·1, 11·6, 17·8, 22·5, and 16·2). The semicarbazone was very unstable, and became blue in air or when heated.

Heptadeca-trans-2 : 8 : 10-*triene*-4 : 6-*diyn*-1-*ol.*—To a solution of *n*-heptylmagnesium bromide (from 3·8 g. of magnesium and 28·4 g. of *n*-heptyl bromide) in ether (100 c.c.) the above aldehyde (6·9 g.) in benzene (200 c.c.) was added during ½ hr. at room temperature with stirring. Stirring was continued for 5½ hr. after which ammonium chloride (18 g.) in water (200 c.c.) was added and the crude product (16·2 g.) isolated in the usual manner. Its solution in toluene (50 c.c.) was added to a boiling solution of toluene-*p*-sulphonic acid (1·62 g.) in toluene (750 c.c.) from which toluene was distilled rapidly. After 15 min. the mixture was cooled, washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated. The residual oil (17·4 g.) was chromatographed on morin–aluminium oxide. The product with the required light absorption (yield, 50%) was eluted with benzene–methanol (100 : 1) and collected in fractions; some of the fractions crystallised, and recrystallisation from light petroleum gave the *triene-diynol* as plates, m. p. 71—71·5° (Found: C, 84·5; H, 9·4. Calc. for $C_{17}H_{22}O$: C, 84·3; H, 9·1%). Light absorption in alcohol: max. at 213, 251, 267, 281, 297, 316, and 338 mμ ($10^{-3}\varepsilon$ 24·3, 32·2, 30·0, 18·3, 29·0, 38·2, and 27·8). A mixture with natural oenanthetol showed no depression of m. p., and the infrared spectra (Nujol) of natural and synthetic materials were identical. In alcohol with palladium–charcoal the synthetic compound absorbed 7·1 mols. of hydrogen.

Toxicity Tests.—Albino mice (30—60 g.) were treated by intraperitoneal injection of suspensions of cicutoxin in lecithin–normal saline. Of 5 mice which received 5 mg. of (−)-cicutoxin

per kg., all died within 30—35 min.; of 5 which received 3·5 mg./kg. only 1 died (100 min.). Of 5 which received 2·5 mg. of (±)-cicutoxin per kg., 4 died (30—37 min.), and of 5 which received 1·8 mg./kg. all survived. The racemic material is thus about twice as active as the natural material.

We acknowledge Mr. W. Günther's collaboration in the preparation of deca-2 : 4 : 6-trienal, and thank the University of Cape Town for a scholarship (to S. M.), the Department of Scientific and Industrial Research for a Maintenance Grant (to B. E. H.), and Imperial Chemical Industries Limited for financial assistance.

THE UNIVERSITY, LEEDS, 2. [*Received, February 4th, 1955.*]

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*Experiments on the Synthesis of Azasteroids. Part II.**

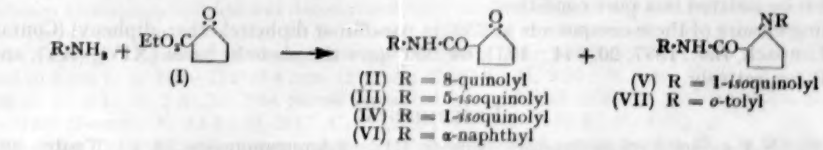
By D. G. BEW and G. R. CLEMO.

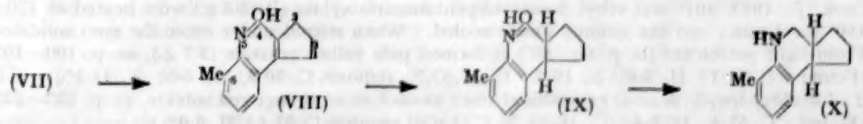
[Reprint Order No. 6104.]

In attempts to synthesise diaza-derivatives of *cyclo*penta[*a*]phenanthrene the condensation of ethyl 2-oxo*cyclo*pentanecarboxylate with some heterocyclic amines has been examined.

ALTHOUGH many nitrogenous steroid derivatives occur in Nature, none has been found in which the hetero-atom is part of the *cyclo*penta[*a*]phenanthrene ring system. Moreover, few of this type have been synthesised. Bolt (*Rec. Trav. chim.*, 1938, **57**, 905) prepared 4-aza-derivatives from natural steroids, and Bachmann and Ramirez (*J. Amer. Chem. Soc.*, 1950, **72**, 2527) prepared lactams from deoxyequilenin and deoxy*iso*equilenin by ring closure of methyl *trans*- and *cis*-1-aminomethyl-1 : 2 : 3 : 4-tetrahydro-2-methylphenanthrene-2-carboxylate. Clemo and Mishra (*J.*, 1953, 192) prepared 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene from α-naphthylamine by condensation with ethyl 2-oxo-*cyclo*pentanecarboxylate (I), and attempts were made to extend this to reaction of the keto-ester with 8-aminoquinoline and 1- and 5-amino*iso*quinoline.

Condensation of 8-aminoquinoline with the keto-ester (I) at 180° gave the amide (II) which gave a deep blue colour with ferric chloride. Reaction of 5-amino*iso*quinoline under





the same conditions formed the amide (III) (Mishra (Ph.D. Thesis, Durham, 1953). Attempts to cyclise these amides to compounds analogous to (VIII) proved unsuccessful. The use of hydrochloric acid (Albert, Brown, and Duewell, *J.*, 1948, 1284), sulphuric acid at temperatures above 60°, or phosphoric oxide and phosphoric acid (Smith, *J.*, 1953, 805) resulted in hydrolysis of the amide group, and small quantities of the parent amines were recovered.

Treatment of 1-amino*iso*quinoline with the keto-ester (I) under the conditions described above gave a mixture of a keto-amide (IV) and an imino-amide (V) : the former, but not the latter, gave a violet colour with ferric chloride. For cyclisation of the keto-amide (IV),

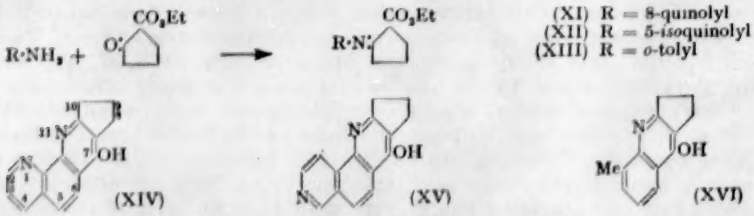
* Part I, *J.*, 1953, 192.

prior reduction of the heterocyclic ring is necessary, but all attempts to effect this resulted in cleavage of the amide bond or recovery of starting material.

Condensation of 5-amino-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline, prepared by reduction of 5-amino*iso*quinoline methiodide (cf. Barltrop and Taylor, *J.*, 1951, 108), with the keto-ester (I) was also examined as it was thought that position 6 would thus be activated towards dehydrating agents. A red-brown gum was obtained which was insoluble in ether and could not be purified by distillation and on treatment with the reagents mentioned above merely afforded small amounts of 5-amino-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline. Since Clemo and Mishra (*loc. cit.*) were able to cyclise the naphthalide (VI) it appears that the influence of the heterocyclic nitrogen atom weakens the amide link, which is thus readily hydrolysed.

In view of this, *o*-toluidine was condensed with the keto-ester (I). The product gave no colour with ferric chloride and was the imino-amide (VII). Treatment with sulphuric acid cyclised it to 2 : 3-dihydro-4-hydroxy-6-methyl*cyclo*penta[*c*]quinoline (VIII). Reduction with sodium amalgam in boiling ethanol formed the tetrahydro-compound (IX) and further reduction with lithium aluminium hydride gave the hexahydro-compound (X). Attempts to use the 6-methyl group as the starting point in the synthesis of a second heterocyclic ring have not yet succeeded.

Reaction of the keto-ester (I) with amines under reflux in alcoholic solution results in the formation of imino-esters: under these conditions the Schiff's bases (XI), (XII), and



(XIII) were obtained. Ethyl 2-8′-quinolylimino*cyclo*pentanecarboxylate (XI) gave no picrate, and treatment with methyl iodide gave an unstable dimethiodide. The imino-ester (XII) gave a crystalline picrate; the ester (XIII) from *o*-toluidine gave no picrate, nor could it be isolated in a pure condition.

Ring closure of these compounds at 250° in paraffin or diphenyl ether–diphenyl (Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1931, **64**, 969) gave the phenolic bases (XIV), (XV), and (XVI) respectively.

Experimental

2-*Oxo*-N-8′-*quinolyl*cyclo*pentanecarboxyamide* (II).—8-Aminoquinoline (5 g.) (Coates and Cook, *J.*, 1943, 401) and ethyl 2-oxo*cyclo*pentanecarboxylate (I) (5·5 g.) were heated at 170—180° for 4 min., and the gummy *amide* cooled. When stirred under ether the gum solidified. From light petroleum (b. p. 60—80°) it formed pale yellow crystals (3·7 g.), m. p. 100—102° (Found: C, 71·1; H, 5·6; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as an orange-red solvate, m. p. 232—235° (Found: C, 57·4; H, 5·1. $C_{21}H_{18}O_5N_6,C_2H_5{\cdot}OH$ requires C, 57·6; H, 5·0%).

2-*Oxo*-N-5′-*iso*quinolyl*cyclo*pentanecarboxyamide* (III).—5-Amino*iso*quinoline (5 g.) (Misani and Bogert, *J. Org. Chem.*, 1945, **10**, 358) and the keto-ester (I) (5·5 g.) were condensed and worked up as described above. The solid *product* crystallised from benzene or alcohol as colourless plates (3·9 g.), m. p. 120—122° (Found: C, 71·1; H, 5·9; N, 11·3. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·1%). The *picrate* crystallised from alcohol as yellow needles, m. p. 210—214° (decomp.) (Found: C, 52·3; H, 3·7. $C_{21}H_{17}O_9N_5$ requires C, 52·4; H, 3·5%).

2-*Oxo*-N-1′-*iso*quinolyl*cyclo*pentanecarboxyamide* (IV).—1-Amino*iso*quinoline (7 g.) (Bergström *et al.*, *ibid.*, 1946, **11**, 239) and the keto-ester (I) (7·6 g.), condensed as described above, gave a yellow-brown solid product which was extracted with cold methanol to give a yellow solution. After treatment with charcoal and concentration, this deposited the yellow *amide* (IV) (3·7 g.), m. p. 176—178° (Found: C, 70·6; H, 5·8; N, 11·6. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H,

5·5; N, 11·1%). The *picrate* crystallised as prisms (from ethanol), m. p. 177—180° (Found: C, 52·7; H, 3·7. $C_{21}H_{17}O_8N_5$ requires C, 52·4; H, 3·5%).

N-1′-iso*Quinolyl*-2-1′-iso*quinolyliminocyclopentanecarboxyamide* (V), the solid residue from the methanol extraction of the above product and from ethanol, formed pale straw-coloured prisms (0·6 g.), m. p. 183—185° (Found: C, 76·3; H, 5·4; N, 14·4. $C_{24}H_{20}ON_4$ requires C, 75·9; H, 5·3; N, 14·7%).

5-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*isoquinoline.—A solution of 5-aminoisoquinoline methiodide (10 g.) and diethylamine (9 ml.) in methanol (120 ml.) was hydrogenated over Raney nickel at 150°/80 atm. for 3 hr. The catalyst was filtered off and the solvent removed. Distillation of the gummy residue gave the *base* as a pale yellow liquid (4·9 g.), b. p. 139—142°/0·1 mm. (Found: C, 74·1; H, 8·8; H, 16·9. $C_{10}H_{14}N_2$ requires C, 74·2; H, 8·6; N, 17·2%). It gave a *dipicrate*, m. p. 177—179° (from ethanol) (Found: C, 42·8; H, 3·6. $C_{22}H_{20}O_{14}N_8$ requires C, 42·6; H, 3·2%).

N-o-*Tolyl*-2-o-*tolyliminocyclopentanecarboxyamide* (VII).—o-Toluidine (10 g.) and the keto-ester (I) (15 g.) were heated at 170—180° for 5 min. The melt solidified on cooling and was extracted with cold methanol to give a brown solution. Treatment of the methanol extract with charcoal gave a yellow solution which deposited the *imino-amide* (VII) as long, pale yellow needles (16 g.), m. p. 131—133° (Found: C, 78·3; H, 7·5; N, 9·5. $C_{20}H_{22}ON_2$ requires C, 78·5; H, 7·2; N, 9·15%).

2 : 3-*Dihydro*-4-*hydroxy*-6-*methyl*cyclo*penta*[c]*quinoline* (VIII).—The toluidide (VII) (8 g.) was added slowly to cooled sulphuric acid (15 ml.) with stirring. The mixture was heated on a water-bath until the vigorous reaction had ceased and then for a further 10 min. The deep brown liquid was poured on crushed ice (400 g.) and made alkaline with 20% sodium hydroxide solution, and the solid was collected. Recrystallisation of the precipitated solid from alcohol gave the cyclo*pentaquinoline* (VIII) as colourless plates (4·6 g.), m. p. 254—256° (Found: C, 78·3; H, 6·7; N, 7·2. $C_{13}H_{13}ON$ requires C, 78·45; H, 6·5; N, 7·1%).

2 : 3 : 3a : 9b-*Tetrahydro*-4-*hydroxy*-6-*methyl*cyclo*penta*[c]*quinoline* (IX).—The base (VIII) (3 g.) and sodium hydrogen carbonate (1 g.) in alcohol (120 ml.) were heated on a water-bath with vigorous stirring. Sodium amalgam (160 g.; 4%) was added in portions during 4 hr., and the stirring and heating were continued for a further 5 hr. The solution was filtered whilst hot and the filtrate evaporated to dryness. Extraction of the residue with benzene gave, after concentration of the extract, the *tetrahydro-compound* (IX) as colourless prisms (2 g.), m. p. 129—131° (Found: C, 77·7; H, 7·7; N, 6·5. $C_{15}H_{15}ON$ requires C, 77·7; H, 7·5; N, 6·95%).

2 : 3 : 3a : 4 : 5 : 9b-*Hexahydro*-6-*methyl*cyclo*penta*[c]*quinoline* (X).—A solution of the above base (IX) (1 g.) in ether (40 ml.) was added to a cooled ethereal solution of lithium aluminium hydride (15 ml.; 80-vol.). The mixture was refluxed for 6 hr., then set aside overnight. Excess of lithium aluminium hydride was decomposed with crushed ice, and the ether layer separated. The aqueous solution was extracted twice with ether and the combined ether solutions were dried (Na_2SO_4). Removal of the solvent gave a brown *base* which distilled as a pale yellow liquid (0·8 g.), b. p. 109—112°/0·4 mm. (Found: C, 83·5; H, 9·05; N, 7·8. $C_{13}H_{17}N$ requires C, 83·5; H, 9·1; N, 7·5%). The *picrate* separated from ethanol as bright yellow prisms, m. p. 177—180° (Found: C, 54·6; H, 5·1. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8%).

Ethyl 2-8′-*Quinolyliminocyclopentanecarboxylate* (XI).—8-Aminoquinoline (5 g.), the keto-ester (I) (5·5 g.), and hydrochloric acid (2 drops; 1 : 1) in ethanol (25 ml.) were refluxed for 6 hr. The solvent was distilled off, and the gummy residue stirred under ether and kept in a refrigerator overnight. Crystallisation of the now solid residue from ethanol gave orange prisms (4·9 g.), m. p. 86—87° (Found: C, 72·6; H, 6·6; N, 10·4. $C_{17}H_{16}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%). Treatment with methyl iodide in acetone at 80° in a sealed tube gave unstable red crystals, m. p. 188—190° (Found: C, 40·2; H, 3·95. $C_{17}H_{16}O_2N_2,2CH_3I$ requires C, 40·3; H, 4·25%).

9 : 10-*Dihydro*-7-*hydroxy*-1 : 11-*diaza*cyclo*penta*[b]*phenanthrene* (XIV).—The imino-ester (XI) (4 g.) was added to hot diphenyl ether–diphenyl (60 ml.) with stirring and the temperature raised to 250° for 10 min. The cooled solution was filtered and the brown residue washed well with benzene. Crystallisation from alcohol (charcoal) gave the *diaza-compound* as pale yellow needles (2·2 g.), m. p. 265—268° (Found: C, 76·2; H, 5·3; N, 11·6. $C_{15}H_{12}ON_2$ requires C, 76·4; H, 5·1; N, 11·9%). Its *picrate* crystallised from ethanol as bright yellow leaflets, m. p. 233—237° (decomp.) (Found: C, 54·0; H, 3·4. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·2%).

Ethyl 2-5′-iso*Quinolyliminocyclopentanecarboxylate* (XII).—Reaction of 5-aminoisoquinoline (5 g.) as in the preceding case yielded the *imino-ester* (5·6 g.), m. p. 123—125° (from ethanol) (Found: C, 72·6; H, 6·1; N, 10·3. $C_{17}H_{16}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%). The

picrate crystallised from alcohol as orange-yellow rhombohedra, m. p. 189—191° (Found : C, 54·1; H, 4·4. $C_{22}H_{11}O_9N_5$ requires C, 54·0; H, 4·1%).

9 : 10-*Dihydro-7-hydroxy-3* : 11-*diaza*cyclo*penta*[b]*phenanthrene* (XV).—The Schiff's base (XII) (5 g.) was cyclised as described for (XI). After being washed with benzene the crude *diaza-compound* crystallised from ethanol as white needles (2·9 g.), m. p. 323—326° (Found : C, 76·1; H, 5·5; N, 11·7. $C_{15}H_{12}ON_2$ requires C, 76·4; H, 5·1; N, 11·9%). The *picrate* formed yellow prisms, m. p. 265—270° (decomp.) from alcohol (Found : C, 54·5; H, 3·6. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·2%).

2 : 3-*Dihydro-9-hydroxy-5-methyl*cyclo*penta*[b]*quinoline* (XVI).—A solution of *o*-toluidine (5 g.), the keto-ester (I) (7·5 g.), and hydrochloric acid (2 drops; 1 : 1) in ethanol (25 ml.) was refluxed for 6 hr. After removal of the solvent, the gummy residue was added to a 1 : 3 mixture (50 ml.) of diphenyl and diphenyl ether at 100° and then heated at 250° with stirring for 10 min. The solution was cooled, and the brown solid product collected, washed with benzene and crystallised from alcohol. The *base* (XVI) was isolated as a white solid (3 g.), m. p. 307—310° (decomp.) (Found : C, 78·6; H, 6·7; N, 7·3. $C_{13}H_{11}ON$ requires C, 78·45; H, 6·5; N, 7·05%).

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King's College, Newcastle-on-Tyne, 1. [*Received, February 8th*, 1955.]

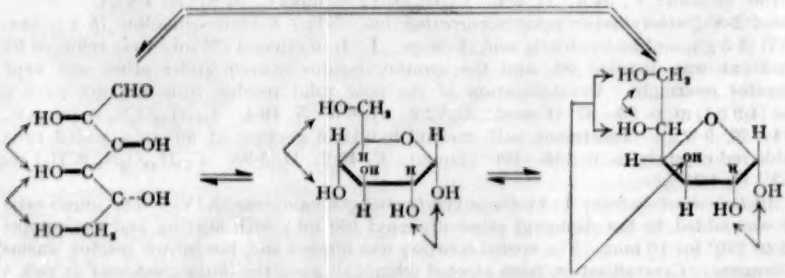
Ionophoresis of Carbohydrates. Part II. Some Pyranose and Furanose Derivatives of* D-*Glucose.*

By A. B. Foster and M. Stacey.

[Reprint Order No. 6131.]

Ionophoresis in alkaline borate buffer of a series of D-glucopyranoside and D-glucofuranoside derivatives has been studied. Hitherto unrecognized reactions between these derivatives and borate ions have been observed. The results obtained give some information about the equilibrium of reducing forms of D-glucose in aqueous alkaline borate solution.

In Part I * evidence was presented which indicated that the reaction of reducing sugar derivatives with borate ions in the aqueous alkaline media used in filter-paper ionophoresis was more complex than that reported to occur in aqueous solutions of boric acid (Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189). Thus it appeared that of the cyclic and open-chain forms of the reducing sugar derivatives in equilibrium in aqueous solution, the latter forms (see formulæ) reacted most strongly with borate ions. Other, hitherto unrecognized interactions have now been observed and are described herein.



Representation of part of the equilibrium of the reducing forms of D-*glucose in solution. The β-pyranose and β-furanose forms are not included.*

In order to limit the possibilities for reaction of reducing sugar derivatives with borate ions, a series of D-glucose derivatives has been studied in which the ring type was fixed (for

* Part I, *J.*, 1953, 982.

a preliminary report see Foster and Stacey, Abs. Papers, Amer. Chem. Soc. Meeting, New York, September, 1954). As in Part I, M_G values (rates of migration compared with that of D-glucose) have been taken as measures of borate-ion interaction.

Pyranose Derivatives.—The M_G values of a series of derivatives of D-glucopyranose are listed in Table 1. This shows that methyl α- and β-D-glucopyranoside have a definite, though weak, interaction, approximately in the ratio 1 : 2. The M_G values of the derivatives (V—VIII) indicate that the 2- and 3-hydroxyl groups are not involved in complex formation whereas the zero M_G values of the derivatives (IX—XIII) indicate the complex to be formed across the 4 : 6-hydroxyl groups in the glucopyranosides (I) and (II). There is here a further analogy between the reaction of borate ions and of benzaldehyde with carbohydrates (cf. Part I) [condensation of benzaldehyde with (I) or (II) to give a 4 : 6-*O*-benzylidene derivative is well known]. A further analogy is the condensation of phenyl phosphorodichloridate with methyl α-D-glucopyranoside to give a 4 : 6-(hydrogen phosphate) (Baddiley, Buchanan, and Szabó, *J.*, 1954, 3826).

The wide difference (0·08) in the M_G values of methyl α- (I) and β-D-glucopyranoside (II) was unexpected. In the preferred conformation of the β-anomer all the non-protonic substituents are in equatorial positions round the pyran ring, but the α-anomer has the glycosidic methoxyl group in an axial position where it may impede the movement of borate ions across one face of the molecule. This is reflected in the lower M_G value of the α-anomer (I). That the glycosidic methoxyl group in the β-anomer (II) does not impede the approach of borate ions is indicated by the M_G values of 1 : 5-anhydro-D-glucitol (IV) and 1 : 5-anhydro-2-deoxy-D-glucitol (V) which are close to that of the β-glucoside (II). Non-protonic substituents are absent from $C_{(1)}$ in the anhydro-compounds (IV) and (V). The remoteness of the glycosidic methoxyl group and the groups on $C_{(4)}$ and $C_{(5)}$ in the α-anomer (I) precludes hydrogen bonding which reduces their availability for complex formation. Thus the difference in M_G values of the α- and β-anomers (I) and (II) appears to be a simple steric effect. It is of interest that the M_G value of the 2-deoxyglycoside (VII) is unexpectedly high.

In the trehaloses, which comprise two D-glucopyranose residues mutually substituted at the glycosidic centres, the operation of a simple steric effect would suggest a series of increasing M_G values $\alpha\alpha < \alpha\beta < \beta\beta$. From the results in Table 1, movement of ββ-trehalose appears to be anomalously slow: effects other than simple steric ones appear to be operating here. Other apparently anomalous results have been observed in the reducing disaccharides (cf. Part I), thus maltose (1–4α) and cellobiose (1–4β) migrate at different rates in ionophoresis (M_G 0·32 and 0·28 respectively), as do *iso*maltose (1–6α, M_G 0·69) and gentiobiose (1–6β, M_G 0·75). These effects are being further investigated.

TABLE 1. *M_G values of derivatives of* D-*glucopyranose.*

Derivative	M_G	Derivative	M_G
Methyl α-D-glucopyranoside (I)	0·11	1 : 6-Anhydro-β-D-glucopyranose (β-glucosan) (X)	0·00
Methyl β-D-glucopyranoside (II)	0·19	Methyl α-D-xylopyranoside (XI)	0·00
Ethyl α-D-glucopyranoside (III)	0·17	Methyl β-D-xylopyranoside (XII)	0·00
1 : 5-Anhydro-D-glucitol (IV)	0·20	1 : 5-Anhydro-D-xylitol (XIII)	0·00
1 : 5-Anhydro-2-deoxy-D-glucitol (V)	0·20	αα-Trehalose (XIV)	0·19
Methyl 2-deoxy-α-D-glucopyranoside (VI)	0·12	αβ-Trehalose (XV)	0·23
Ethyl 2-deoxy-α-D-glucopyranoside (VII)	0·17	ββ-Trehalose (XVI)	0·19—0·20
Ethyl 2 : 3-dideoxy-α-D-glucopyranoside (VIII)	0·10	Sucrose (XVII)	0·17
Methyl 4-*O*-methyl-β-*D*-glucopyranoside (IX)	0·00		

Furanose Derivatives.—Precise formulation of the interaction of derivatives of D-glucofuranose with borate ions is hindered by lack of suitable compounds. The M_G values recorded in Table 2 indicate the occurrence of interactions much stronger than in the

TABLE 2. *M_G values of derivatives of* D-*glucofuranose and* D-*xylofuranose.*

Derivative	M_G	Derivative	M_G
Methyl α-D-glucofuranoside (XVIII)	0·73	1 : 2-*O*-*iso*Propylidene-α-D-glucofuranose (XXI)	0·73
Ethyl α-D-glucofuranoside (XIX)	0·70	Methyl α-D-xylofuranoside	0·30
Ethyl β-D-glucofuranoside (XX)	0·65	Methyl β-D-xylofuranoside	0·30

corresponding pyranose derivatives (I) and (II). The M_G value of 1 : 2-*O*-*iso*propylidene-D-glucofuranose (XXI) reveals that the 2-hydroxyl group is not appreciably involved in complex formation. A weak interaction across the 5 : 6-hydroxyl groups would be expected on analogy with propane-1 : 2-diol (M_G 0·2), so that a further strong interaction must be operating which appears to involve the 3-hydroxyl group with either or both of the 5- and 6-hydroxyl groups. The M_G values (both 0·30) of methyl α- and β-D-xylofuranoside indicate that complex formation does occur across the 3 : 5-hydroxyl groups. The considerable difference in M_G values between these xylofuranosides and the glycofuranose derivatives (XVIII—XXI) suggests that complex formation across the 3 : 6-hydroxyl groups may occur in the latter group.

The interaction of reducing sugar derivatives with borate ions in aqueous alkali is complicated by equilibration of furanose, pyranose, and open-chain forms, any or all of which may be involved in complex formation. In the reducing derivatives of D-glucose (cf. Part I) this equilibrium may be affected, first, by the intensity of interaction of each form with borate ions and, secondly, by substitution of the hydroxyl groups; *e.g.*, protection of the 4- or 5-hydroxyl group precludes the formation of furanose and pyranose forms respectively. The M_G values recorded so far and the interactions known to occur in solutions of boric acid (Böeseken, *loc. cit.*), which are presumed to be intensified in the presence of alkali, lead to the complexes shown in the formulæ (p. 1778). For the α-furanose form it is not possible in alkaline borate solutions to obtain a measure of the contribution of the 1 : 2-hydroxyl groups alone since the 4-hydroxyl group must be simultaneously unprotected, and hence complex formation across the 2 : 4-hydroxyl groups in the open-chain form is also possible. The M_G values for 3 : 4-di-*O*-methyl-D-glucose (0·31) must largely originate from the 1 : 2-hydroxyl groups in the α-pyranose form (see formulæ). Although, from the results in Table 2, the furanose forms of D-glucose are seen to form firm complexes elsewhere than at the 1 : 2-hydroxyl groups, these forms appear to be minor contributors to the equilibrium. This is indicated by (*a*) the low M_G value (0·23) of 2-*O*-methyl-D-glucose for which a firm complex across the 2 : 4-hydroxyl groups in the open-chain form is prelcuded but complexes across the 3 : 5 : 6-hydroxyl groups of the furanose forms are possible, and (*b*) the high M_G value (0·82) of 3-*O*-methyl-D-glucose where the reverse is the case. That the 3 : 5 : 6-hydroxyl groups are involved to some extent in complex formation is indicated by the M_G value (0·12) of 2 : 3-di-*O*-methyl-D-glucose, where this type of complex is precluded, compared with that of 2-*O*-methyl-D-glucose (0·23), where it can occur.

The M_G values reported here and in Part I also indicate that the type of complex formation between borate ions and the reducing forms of the D-glucose derivatives is apparently too weak to disturb appreciably the equilibrium shown in the formulæ. If this were not so, a much higher M_G value for 2-*O*-methyl-D-glucose would be expected, where only the furanose forms can interact strongly with borate ions. Böeseken (*loc. cit.*) observed that the rate of mutarotation of the α- or β-form of D-glucopyranose is not appreciably affected in aqueous boric acid, although as mutarotation proceeds complex formation decreases and increases respectively.

From the ionophoretic studies on derivatives of D-glucose the significant fact emerges that in alkaline borate solution *all* the hydroxyl groups appear to be involved in complex formation to a greater or smaller extent, whereas in aqueous boric acid (Böeseken, *loc. cit.*) only the 1 : 2-hydroxyl groups in the α-pyranose and α-furanose forms are involved.

Ionophoresis of the series of 1–6α-linked D-gluco-oligosaccharides in alkaline borate buffer, where fast migration has been observed, reveals that the lower members may be separated. After ionophoresis at 900 V for 3 hr. (see Experimental section), separation was complete and the M_G values, D-glucose 1·00, *iso*maltose 0·69, *iso*maltotriose 0·57, *iso*maltotetraose 0·50, were observed. Similar results would be expected in the series of 1–6β- and 1–3-linked D-gluco-oligosaccharides. In the series of 1–4α-linked D-gluco-oligosaccharides, where slow migration occurs, M_G values decreased from 0·32 to 0·28 as the molecular size increased from maltose to maltohexaose, and no separation could be obtained. Similar results would be expected in the series of 1–4β- and 1–2-linked D-gluco-oligosaccharides [sophorose, a 1–2β-linked D-glucodisaccharide, has a low M_G value (0·23)].

Northcote (*Biochem. J.*, **1954**, **58**, 353) has reported the mobilities of a series of amylose and amylopectin preparations in borate buffer at pH 9·2. Amylopectin was observed to migrate faster than amylose, which itself had an appreciable rate of migration. It is possible that the mobility of these polysaccharides is due, in part at least (amylopectin is known in certain cases to contain a small number of phosphate groups), to charges conferred on the molecules by complex formation of the type shown to occur in methyl α- and β-D-glucopyranoside. This would be expected to occur at the non-reducing ends of the chains and in this respect amylopectin, because of its highly branched nature and consequently larger number of non-reducing end-groups, would be expected to form firmer complexes than amylose. In view of the mobility of amylose, other types of complex formation at present unrecognized may also operate.

Experimental

The apparatus and technique for ionophoresis have been described by Foster (*Chem. and Ind.*, 1952, 1050). Ionophoreses were carried out on Whatman No. 3 paper in 0·2M-sodium borate at pH 10 under potentials of 900—1500 v, which gave final currents of 25—40 milliamps. Non-reducing sugar derivatives were located on the ionophoretograms by the use of ammoniacal silver nitrate. The durations of ionophoreses mentioned in the discussion refer to these conditions.

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Chemistry Department, The University,
Edgbaston, Birmingham, 15. [*Received, February 14th*, 1955.]

The Synthesis and Reactions of Branched-chain Hydrocarbons. Part VIII. The Pinacol Rearrangement of an Aliphatic Tetraol.*

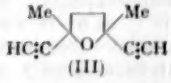
By M. F. Ansell, W. J. Hickinbottom, and A. A. Hyatt.

[Reprint Order No. 6136.]

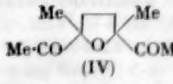
An attempted preparation of **2 : 3 : 6 : 7**-tetramethyloctane-**2 : 3 : 6 : 7**-tetraol is described, together with the preparation and pinacol rearrangement of **2 : 3 : 8 : 9**-tetramethyldecane-**2 : 3 : 8 : 9**-tetraol.

Saturated aliphatic tetratertiary diglycols [*e.g.*, (I)] have not been previously prepared. An attempt was made to obtain **2 : 3 : 6 : 7**-tetramethyloctane-**2 : 3 : 6 : 7**-tetraol (I; n = 2) from **3 : 6**-dimethylocta-**1 : 7**-diyne-**3 : 6**-diol (II) (Milas, Brown, and Phillips, *J. Amer. Chem. Soc.*, 1948, **70**, 2862) by the method of Hickinbottom, Hyatt, and Sparke (*J.*, 1954, 2529, 2533). Hydration of this compound did not yield the desired diketol but gave instead **2 : 5**-diacetyltetrahydro-**2 : 5**-dimethylfuran (IV) whose structure was shown by its formation when the diethynylfuran (III) (Milas, Brown, and Phillips, *loc. cit.*) was

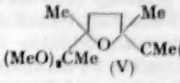
(I) $HO\cdot CMe_2\cdot CMe(OH)\cdot[CH_2]_n\cdot CMe(OH)\cdot CMe_2\cdot OH$ $[HC{\equiv}C\cdot CMe(OH)\cdot CH_2\cdot]_2$ (II)



(III)



(IV)



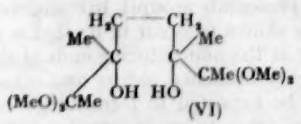
(V)

hydrated with mercuric sulphate in aqueous sulphuric acid. In an attempt to avoid furan formation the addition of methyl alcohol to **3 : 6**-dimethylocta-**1 : 7**-diyne-**3 : 6**-diol (II) under catalysis by boron trifluoride was investigated. This reaction however gave a mixture of the required diol (VI) and the furan derivative (V). The latter was also obtained by the addition of methyl alcohol to the diacetylene (III) in presence of boron trifluoride. Both of these ketals on hydrolysis with dilute acid gave **2 : 5**-diacetyltetrahydro-**2 : 5**-dimethylfuran (IV).

An alternative route to **2 : 3 : 6 : 7**-tetramethyloctane-**2 : 3 : 6 : 7**-tetraol that would minimise the possibility of furan formation is hydrogenation of **2 : 3 : 6 : 7**-tetramethyloct-4-yne-**2 : 3 : 6 : 7**-tetraol. The latter compound could not be prepared either by reaction

* Part VII, *J.*, 1955, 1592.

of acetylene with 3-hydroxy-3-methylbutan-2-one (Favorski and Onischenko, *J. Gen. Chem. U.S.S.R.*, 1941, **11**, 1111) or by condensation of 2 : 3-dimethylpent-4-yne-2 : 3-diol (Ansell, Hickinbottom, and Hyatt, *J.*, 1955, 1592) with 3-hydroxy-3-methylbutan-2-one in the presence of sodamide in liquid ammonia.



(VI)

HO·CMe$_2$·CMe(OH)·C$_2$CH (VII)

[HO·CMe$_2$·CMe(OH)·C$_2$C·]$_2$ (VIII)

(Me·CO·CMe$_2$·CH$_2$·CH$_2$·)$_2$ (IX)

Attention was then directed to the synthesis of 2 : 3 : 8 : 9-tetramethyldecane-2 : 3 : 8 : 9-tetraol (I; $n = 4$). It was found that 2 : 3-dimethylpent-4-yne-2 : 3-diol (VII) (Ansell *et al., loc. cit.*) undergoes oxidative dimerisation with oxygen in the presence of cuprous chloride–ammonium chloride solution to produce 2 : 3 : 8 : 9-tetramethyldeca-4 : 6-diyne-2 : 3 : 8 : 9-tetraol (VIII) in good yield (cf. Zal'kind and Aizikovitch, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 227). The latter was obtained in *meso*- and racemic forms. It was readily hydrogenated to the *meso*- and racemic forms of 2 : 3 : 8 : 9-tetramethyldecane-2 : 3 : 8 : 9-tetraol (I; $n = 4$), the structure of which was established by oxidation to octane-2 : 6-dione and acetone. The tetraol (I; $n = 4$) rearranges on dissolution in concentrated sulphuric acid at −10° and subsequent dilution, to give 3 : 3 : 8 : 8-tetramethyldecane-2 : 9-dione (IX). The structure of the dione was established by its non-identity with 2 : 2 : 9 : 9-tetramethyldecane-3 : 8-dione (Fuson and Robinson, *J. Amer. Chem. Soc.*, 1940, **62**, 358) which is a possible product of the rearrangement, and by its oxidation to 2 : 2 : 7 : 7-tetramethylsuberic acid.

The formation of the dione (IX) is the first recorded example, as far as we are aware, of a tetraol undergoing two simultaneous pinacol–pinacolone rearrangements.

Experimental

Hydration of 3 : 6-*Dimethylocta*-1 : 7-*diyne*-3 : 6-*diol*.—The diyne (83 g.) (Milas, Brown, and Phillips, *loc. cit.*) was added in small portions during 1 hr. to a stirred, boiling solution of mercuric oxide (4·5 g.) in 10% sulphuric acid (300 c.c.). After a further hour's heating and stirring the mixture was steam-distilled. The upper layer of the distillate, combined with the ethereal extracts of the lower layer, was washed with water, dried ($MgSO_4$), and distilled, yielding 2 : 5-*diacetyltetrahydro*-2 : 5-*dimethylfuran* (22·5 g.), b. p. 87—88°/2 mm., n_D^{20} 1·4506 (Found: C, 65·5; H, 8·7. $C_{10}H_{16}O_3$ requires 65·2; H, 8·7%). Its *bis*-2 : 4-*dinitrophenylhydrazone*, yellow needles from pyridine, has m. p. 212° (Found: C, 48·5; H, 4·3; N, 20·4. $C_{22}H_{24}O_9N_8$ requires C, 48·5; H, 4·4; N, 20·5%), and its *disemicarbazone* (purified by boiling with ether and benzene), m. p. 214° (Found: C, 48·5; H, 7·4; N, 28·0. $C_{12}H_{22}O_3N_6$ requires C, 48·3; H, 7·4; N, 28·2%).

2 : 5-*Diethynyl- and* 2 : 5-*Diacetyltetrahydro*-2 : 5-*dimethylfuran*.—3 : 6-Dimethylocta-1 : 7-diyne-3 : 6-diol (10 g.) was heated at 80° with 10% sulphuric acid (50 c.c.) for 2 hr. After cooling, the organic material was extracted with ether and washed with water. Distillation of the dried ($MgSO_4$) ethereal extract gave 2 : 5-diethynyltetrahydro-2 : 5-dimethylfuran, b. p. 62—64°/17 mm., n_D^{20} 1·4559 (Found: C, 80·9; H, 8·4. Calc. for $C_{10}H_{12}O$: C, 81·0; H, 8·2%). Milas, Brown, and Phillips, (*loc. cit.*) record b. p. 63·5—65°/28 mm., n_D^{20} 1·4790. Hydration of this diyne as for 3 : 6-dimethylocta-1 : 7-diyne-3 : 6-diol gave 2 : 5-diacetyltetrahydro-2 : 5-dimethylfuran, b. p. 55°/0·5 mm., n_D^{20} 1·4490.

2 : 2 : 7 : 7-*Tetramethoxy*-3 : 6-*dimethyloctan*-3 : 6-*diol and* 2 : 5-*Di*-(1 : 1-*dimethoxyethyl*)*tetrahydro*-2 : 5-*dimethylfuran*.—A mixture of mercuric oxide (5 g.), boron trifluoride–ether complex (5 c.c.) (Hennion, Hinton, and Nieuwland, *J. Amer. Chem. Soc.*, 1933, **55**, 2857), dry methanol (5 c.c.), and trichloroacetic acid (1 g.) was heated for 1 min., and then dry methanol (200 g.) was added. To this stirred solution was added 3 : 6-dimethylocta-1 : 7-diyne-3 : 6-diol (112 g.) in dry methanol (300 g.) at such a rate that the temperature was kept at 45—55°. After further stirring (3 hr.) anhydrous potassium carbonate (10 g.) was added, and the mixture kept overnight. The supernatant liquid was decanted off, excess of methanol removed, and the residue distilled, yielding, with a small fore-run and intermediate cuts: (*a*) 2 : 5-*di*-(1 : 1-*dimethoxyethyl*)*tetrahydro*-2 : 5-*dimethylfuran* (87·0 g.), b. p. 62°/1·2 mm., m. p. 42° (after vacuum-sublimation) (Found: C, 60·6; H, 10·5; active H, 0. $C_{14}H_{28}O_5$ requires C, 60·8; H, 10·2%), also obtained

from the diacetylenic furan by the same procedure; (*b*) **2 : 2 : 7 : 7-*tetramethoxy*-3 : 6-*dimethyl*-*octane*-3 : 6-*diol*** (88·3 g.), b. p. 92°/0·7 mm., n_D^{20} 1·4635 (Found: C, 57·3; H, 10·1; active H, 0·61. $C_{14}H_{30}O_6$ requires C, 57·1; H, 10·3; active H, 0·68%).

Hydrolysis of either ketal by shaking it with excess of cold 2% sulphuric acid gave **2 : 5-di**acetyltetrahydro-**2 : 5-dimethylfuran**, identified by comparison of its derivatives with those prepared above.

Attempted Preparation of **2 : 3 : 6 : 7-*Tetramethyloct*-4-*yne*-2 : 3 : 6 : 7-*tetraol***.—(*a*) (cf. Favorski and Onischenko, *loc. cit.*). Acetylene was passed into an ice-cold stirred suspension of potassium hydroxide flakes (84 g.) in dry ether (800 c.c.). After 20 min. 3-hydroxy-3-methylbutan-2-one (51 g.) was added during ½ hr. Passage of acetylene was continued for a further 6 hr., and the mixture left overnight. Water was then added to the cold mixture to dissolve the solid, and the ether layer was separated and combined with the ethereal extract of the aqueous layer. The combined extracts were saturated with carbon dioxide, and the precipitated solid was filtered off. After drying ($MgSO_4$), the ether was removed and the residue distilled, yielding 3-hydroxy-3-methylbutan-2-one (18 g.) (collected in cold traps) and **2 : 3-dimethylpent-4-yne-2 : 3-diol** (23 g.), b. p. 55—56°/0·9 mm., n_D^{20} 1·4620. The residue, a viscous liquid did not solidify, was unsaturated, and was assumed to be mainly condensation products of the ketol.

(*b*) **2 : 3-Dimethylpent-4-yne-2 : 3-diol** (128 g., 1 mole) was added during ½ hr. to a well-stirred suspension of sodamide (4 moles) in liquid ammonia (2 l.). After 1 hr. 3-hydroxy-3-methylbutan-2-one (102 g., 1 mole) was added slowly. One hour later, ammonium chloride (250 g.) was added and stirring continued for a further hour. The ammonia was allowed to evaporate overnight, and then water (2 l.) was added. The organic layer was separated and combined with the ethereal extract of the aqueous layer. After drying ($MgSO_4$), the solvent was removed, and the residue distilled, yielding both starting materials unchanged. The same result was obtained with lithium or sodium amide in boiling ether or benzene.

2 : 3 : 8 : 9-*Tetramethyldeca*-4 : 6-*diyne*-2 : 3 : 8 : 9-*tetraol*.—A slow stream of oxygen was passed through a solution of **2 : 3-dimethylpent-4-yne-2 : 3-diol** (64 g.) (Ansell *et al.*, *loc. cit.*), cuprous chloride (48 g.), and ammonium chloride (144 g.) in water (600 c.c.) for 24 hr. After removal of the precipitate, passage of oxygen was continued until no further solid was deposited. The combined solids were washed with water, dried *in vacuo*, and dissolved in ethyl acetate by Soxhlet extraction. Evaporation of the extract gave **2 : 3 : 8 : 9-tetramethyl-4 : 6-diyne-2 : 3 : 8 : 9-tetraol** (51 g.), m. p. 116—119°, which was purified by washing it with boiling ether and crystallising it from ethyl acetate. The first crop had m. p. 130·5° after recrystallisation. The more soluble material had m. p. 114° after repeated crystallisation from ethyl acetate–light petroleum (b. p. 60—80°). Mixtures of the two fractions melted between 114° and 130·5°. This separation of *meso*- and racemic forms was not pursued; the final purification was effected by recrystallisation of the combined material from ethyl acetate and light petroleum mixtures. The pure material was obtained as cubic crystals, soluble in ethanol or hot water and insoluble in ether, benzene, or light petroleum (Found: C, 62·8; H, 8·8; active H, 1·78%; *M*, 253. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7; active H, 1·59%; *M*, 254). A better analysis could not be obtained.

2 : 3 : 8 : 9-*Tetramethyldecane*-2 : 3 : 8 : 9-*tetraol*. The above diyne (38·1 g.) in ethanol (300 c.c.) was hydrogenated at 50 lb. per sq. in., in the presence of Adams catalyst (0·5 g.) (8 hr.). The precipitate was filtered off, washed with ethanol, and dried. Its m. p. (180°) was raised to 185° after removal of the catalyst and repeated crystallisation from ethanol. Evaporation of the initial filtrate gave a solid of m. p. 140° which was 139—140° after recrystallisation from ethanol–light petroleum (b. p. 60—80°). These two solids are the *meso*- and the racemic form of **2 : 3 : 8 : 9-tetramethyldecane-2 : 3 : 8 : 9-tetraol**. Final purification was effected by recrystallising the combined fractions from ethanol–light petroleum (Found: C, 64·0; H, 11·3%; *M*, 228. Calc. for $C_{14}H_{30}O_4$: C, 64·1; H, 11·5%; *M*, 262).

Oxidative Fission of **2 : 3 : 8 : 9-*Tetramethyldecane*-2 : 3 : 8 : 9-*tetraol***.—Periodic acid (3 g.) was added to a solution of the above tetraol (3 g.) in water (20 c.c.) and methanol (5 c.c.), and the mixture shaken for 4 hr. Air was then aspirated for 3 hr. through the solution into a trap containing a warm solution of **2 : 4-dinitrophenylhydrazine** in aqueous-alcoholic sulphuric acid. The precipitated acetone **2 : 4-dinitrophenylhydrazone** had m. p. and mixed m. p. 125° after recrystallisation from ethanol. The remainder of oxidation product was extracted with ether, the extract evaporated, and the residue treated with **2 : 4-dinitrophenylhydrazine** in aqueous-alcoholic sulphuric acid, yielding octane-2 : 7-dione **2 : 4-dinitrophenylhydrazone** as orange needles, m. p. 218—219° after recrystallisation from ethanol. Shimizu (*J. Agr. Chem. Soc. Japan*, 1950, **23**, 288) records m. p. 219°.

Rearrangement of **2 : 3 : 8 : 9-***Tetramethyldecane*-**2 : 3 : 8 : 9-***tetraol.*—The above tetraol (30 g.) was added during 1 hr. to concentrated sulphuric acid (600 g.) at between −5° and −10°. After a further 3 hours' stirring, the mixture was poured on ice (2 kg.). The precipitated solid was filtered off and the filtrate extracted with ether. The combined organic material was washed with water and dried ($MgSO_4$) and the ether evaporated, yielding pale yellow crystals (22·3 g.) which were dissolved in light petroleum (b. p. 40—60°) and passed through a 6-in. column of activated alumina. Evaporation of the solvent gave colourless crystals (20·8 g.). Recrystallisation from light petroleum (b. p. <40°) gave **3 : 3 : 8 : 8-***tetramethyldecane*-**2 : 9-***dione*, m. p. 63° (Found: C, 74·2; H, 11·3%; *M*, 193. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·6%; *M*, 226). Its *disemicarbazone*, colourless needles from ethanol, had m. p. 228 (Found: C, 56·2; H, 9·6; N, 24·7. $C_{16}H_{32}O_2N_6$ requires C, 56·4; H, 9·5; N, 24·7%), and the *bis*-**2** : **4**-*dinitrophenylhydrazone*, orange-yellow needles from benzene–light petroleum (b. p. 60—80°), had m. p. 204° (Found: C, 53·2; H, 5·8; N, 19·3. $C_{26}H_{34}O_8N_8$ requires C, 53·2; H, 5·8; N, 19·1%) [cf. **2 : 2 : 9 : 9**-tetramethyldecane-**3 : 8**-dione, m. p. 52—52·5° (bis-**2** : **4**-dinitrophenylhydrazone, m. p. 251—252°) (Fuson and Robinson, *loc. cit.*)].

Oxidation of **3 : 3 : 8 : 8-***Tetramethyldecane*-**2 : 9-***dione.*—A well-stirred mixture of the above dione (3 g.), nitric acid (25 c.c.; *d* 1·42), and water (25 c.c.) was heated under reflux for 8 hr., then cooled, the precipitate filtered off, and the filtrate extracted with ether. The combined organic material was extracted repeatedly with aqueous sodium carbonate. After acidification with 5N-sulphuric acid, the solid was extracted with ether, washed with water, and dried ($MgSO_4$). The residue obtained on evaporation of the ether recrystallised from ethyl acetate, yielding **2 : 2 : 7 : 7**-tetramethylsuberic acid, m. p. 185—186° (Found: C, 62·6; H, 9·4%; equiv., 110. Calc. for $C_{12}H_{22}O_4$: C, 62·6; H, 9·6%; equiv., 115). Adams and Anderson (*J. Amer. Chem. Soc.*, 1951, **73**, 136) record m. p. 179—181°.

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UNIVERSITY OF LONDON, QUEEN MARY COLLEGE,
MILE END ROAD, LONDON, E.1. [*Received, February 16th*, 1955.]

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*The Use of Equilibrium Constants to calculcate Thermodynamic Quantities. Part II.**

By K. E. HOWLETT.

[Reprint Order No. 6092.]

Equilibria in the gaseous systems ethyl chloride–ethylene–hydrogen chloride and *iso*propyl chloride–propene–hydrogen chloride have been examined over the temperature ranges 175—255° and 60—210°, respectively. From the variation of the equilibrium constants with temperature the heat and entropy changes accompanying hydrochlorination are derived. The latter changes enable the entropies of the alkyl halides to be found. By comparison with the statistical entropies, the energy barriers hindering free internal rotation in these molecules are obtained and hence the thermodynamic functions are calculated over the range 298—700° K.

A review of previous work on the ethyl chloride system shows that the present results agree most closely with those of Lane, Linnett, and Oswin, and of Gordon and Giauque.

THE published thermochemical and thermodynamic data for chlorohydrocarbons are relatively scanty, and moreover are often conflicting. This arises largely because few determinations of heats of combustion of simple chlorohydrocarbons have been made with an accuracy acceptable by modern standards. The present series of investigations attempts to provide some of this missing information. The equilibria between hydrogen chloride, *iso*butene, and *tert.*-butyl chloride were discussed in Part I.* The present communication deals with the equilibria resulting from the decomposition of ethyl and *iso*propyl chlorides. From the variation of these equilibrium constants with temperature the heat and entropy changes accompanying dehydrochlorination are directly obtained.

* Part I, *J.*, 1951, 1409.

The only previous work on the hydrogen chloride–propene–*iso*propyl chloride system is that briefly mentioned by Wibaut, Diekmann, and Rutgers (*Rec. Trav. chim.*, **1928**, **47**, 477) concerning the reaction products. Ethyl chloride has, however, attracted periodic attention, with various results. Wibaut, Diekmann, and Rutgers (*loc. cit.*) obtained an 84·4% yield of ethyl chloride by synthesis from hydrogen chloride and ethylene over bismuth chloride on asbestos at 200° and 1 atm., whilst Tilman (Thesis, Amsterdam, 1928) reported 4% decomposition of ethyl chloride at 120°. Rudkowskii, Trifel, and Frost (*Ukrain. Chem. J.*, 1935, **10**, 277) measured equilibrium constants in this system over bismuth chloride supported on silica gel at 170°, 200°, and 230° (all ± 2°). Their results may be summarised as $\log_{10} K_p = (13{,}400/4{\cdot}575\,T) - 4{\cdot}96$. (All such equations are quoted here in atm. units, the alkyl halide being considered to be the product.) It was, however, pointed out by Linnett (*Trans. Faraday Soc.*, 1940, **36**, 527) that this equation implies an impossible value for the entropy of ethyl chloride, and in a recent paper Lane, Linnett, and Oswin (*Proc. Roy. Soc.*, 1953, **216**, *A*, 361) have described more accurate determinations in the range 176—218° carried out by a flow method over a supported ferric chloride catalyst (cf. Roush and Morell, U.S.P. 2,110,141). By comparing their results with that of the accurate determination of the entropy of ethyl chloride by Gordon and Giauque (*J. Amer. Chem. Soc.*, 1948, **70**, 1506), Lane, Linnett, and Oswin considered the equilibrium constants to be best expressed as $\log_{10} K_p = (17{,}320/4{\cdot}575\,T) - 6{\cdot}922$.

The heat of formation of ethyl chloride can be estimated in various ways from earlier work. Thus, based on Thomsen's (rather than Berthelot's or Kharasch's) value for the heat of combustion of ethyl chloride, Bichowsky and Rossini ("Thermochemistry of Chemical Substances," Reinhold, New York, 1936) consider $\Delta H_f^\circ{}_{298}$ for ethyl chloride to be 25·7 kcal./mole. Hence, by using a modern value for ΔH_f° for ethylene, the heat of hydrochlorination is calculated to be 16·2 kcal./mole. More recently Casey and Fordham (*J.*, 1951, 2513) have suggested the value 13 ± 2·5 kcal./mole for the heat of hydrochlorination. The heat of reaction may also be estimated from bond-strength determinations. For example, by using Stevenson's table of bond strengths (*J. Amer. Chem. Soc.*, 1943, **65**, 209) obtained by the electron-impact method, the heat of hydrochlorination is calculated to be 16·5 kcal./mole, but this result is dependent upon thermochemical data given by Bichowsky and Rossini (*loc. cit.*). Finally, by use of the approximate method suggested by Conn, Kistiakowsky, and Smith (*J. Amer. Chem. Soc.*, 1938, **60**, 2764), *viz.*, that the heat of hydrochlorination (corrected for ΔH_f° for hydrogen chloride) should be the mean of the heats of hydrogenation and chlorination, the value of 15·9 kcal./mole is found.

Experimental

Apparatus.—The apparatus was similar to that described in Part I. For the decomposition of *tert.*-butyl chloride, glass wool was found to be an effective catalyst, as it is for *tert.*-butyl bromide (Howlett, unpublished work), but glass wool is an inefficient catalyst for inducing decomposition in *iso*propyl chloride and ethyl chloride. A considerable search was made for a suitable catalyst; the static method of measurement imposed some limitation upon its nature. Thus bismuth chloride on silica gel (cf. Rudkowskii, Trifel, and Frost, *loc. cit.*) was found to be far too efficient as an adsorbent. For this reason also, carbon (cf. Lane, Linnett, and Oswin, *loc. cit.*) was avoided and glass wool was finally used as the support. Bismuth and ferric chlorides were tried, but rejected for inefficiency and volatility, respectively.

After considering Cremer's results (*Experientia*, 1948, **4**, 349) on the rates of heterogeneous pyrolysis of ethyl chloride over various metallic chlorides, namely, that the metallic chloride had a marked effect upon both the activation energy and non-exponential term, those materials inducing a reaction of low activation energy and fast rate were investigated. The catalyst eventually employed for both ethyl and *iso*propyl chlorides was a mixture of nickel, cobalt, and a little cadmium chlorides, which was sprayed on to the support in concentrated hydrochloric acid solution, dried *in vacuo* at room temperature, treated with hydrogen chloride, and thereafter maintained *in vacuo* except when in use. This enabled equilibria to be reached in a few hours under all conditions tried, and no appreciable drift in pressure was observed after equilibrium had been established.

Materials.—Commercial *iso*propyl chloride was purified by Barton and Head's method (*Trans. Faraday Soc.*, 1950, **46**, 114). The accepted material had b. p. 34·8° (corr.), n_D^{25} 1·3779.

Commercial ethyl chloride was volatilised in a stream of dry, carbon dioxide-free nitrogen and passed through soda lime and concentrated sulphuric acid traps. The first and last 15% of the distillate were rejected and the middle fraction condensed at −80°. This material was outgassed and its vapour pressure was measured from 0° to 15°. The results, corrected to 0° and standard gravity (980·665 cm. sec.$^{-2}$) by assuming g in this laboratory to be 981·19 cm. sec.$^{-2}$, are given in Table 1. These vapour pressures are closely similar to those obtained in this range by Gordon and Giauque (*loc. cit.*).

TABLE 1.

T	0·30°	2·92°	3·45°	5·90°	8·55°	10·25°	10·47°	11·68°	12·20°	12·35°	12·70°	14·56°
V. p. (mm.)	474·9	527·3	540·0	597·8	661·2	702·5	710·2	740·0	756·6	760·3	770·0	824·2

Results.—The equilibria were approached by decomposition only. Concentrations at equilibrium were measured both by pressure measurements and (particularly for runs in which only small increases in pressure occurred) by condensation of the products at −190° and subsequent titration of the hydrogen chloride. Table 3 shows that these two methods gave similar results. The reaction involving *iso*propyl chloride was studied at total pressures of 50—300 mm. and from 60° to 210°. With ethyl chloride the corresponding figures were 45—140 mm. and 175° to 255°. No variation of equilibrium constant with pressure was observed. This is illustrated in Table 2.

TABLE 2.

	Ethyl chloride at 175·0°					*iso*Propyl chloride at 161·7°			
p_0 (mm.)	29·7	35·7	37·8	53·4	57·7	52·6	70·4	126·7	172·0
K_p	41·5	42·3	40·4	42·8	42·0	18·1	16·7	17·0	17·6

It is well established that equilibria in the ethyl chloride system involve only hydrogen chloride, ethylene, and ethyl chloride, but it was felt desirable to examine the products from *iso*propyl chloride. Accordingly the products from about 50 runs, which had been allowed to reach equilibrium at 161°, were condensed at liquid-air temperature, and combined. The material was slowly warmed to room temperature, the gaseous products were allowed to escape, and the liquid was dried ($CaCl_2$). 9 c.c. of this were refluxed for a few min. and then fractionally distilled. The whole distillate boiled at 34—34·5°, and three fractions of about 3 c.c. each were collected, together with 0·4 c.c. of residue. These fractions had n_D^{17} 1·3796, 1·3797, 1·3800, and 1·3828 respectively. Freshly distilled *iso*propyl chloride has n_D^{17} 1·3796, whilst *n*-propyl chloride (b. p. 46°) has n_D^{17} 1·3900, so this suggests that *n*-propyl chloride is absent from the equilibrium mixture, and furthermore if all the discrepancy in the refractive index of the still residue were due to *n*-propyl chloride, this would constitute 1% of the alkyl chloride present at equilibrium. This possibility has been ignored. The measured equilibrium constants, in atmosphere units, are set out in Table 3. The results may be summarised (by the least-squares method) by the equations:

Ethyl chloride: $\log_{10} K_p = (17{,}440/4{\cdot}575\,T) - 6{\cdot}88_5$

*iso*Propyl chloride: $\log_{10} K_p = (17{,}540/4{\cdot}575\,T) - 7{\cdot}56_3$

compared with the result from Part I:

tert.-Butyl chloride: $\log_{10} K_p = (17{,}700/4{\cdot}575\,T) - 8{\cdot}27$

TABLE 3.

*iso*Propyl chloride									
T°	61·1	61·8^t	79·8^t	79·8^p	99·9^p	111·3^{p,t}	131·9^p	161·7^p	211·3^p
No. of expts. ...	2	1	5	9	6	14	11	4	2
Mean K_p	8595	8290	2040	1950	470	237	81·6	17·35	2·125
Ethyl chloride									
T°	175·0^p	210·4^p	255·8^p						
No. of expts. ...	7	6	3						
Mean K_p	41·8	9·88	2·12						

t, by titration; p, by pressure measurement.

DISCUSSION

The equilibrium constants found for the three hydrochlorination reactions so far studied may be combined with the known rate constants for unimolecular decomposition of the appropriate alkyl chlorides (Barton and Howlett, *J.*, 1949, 165; Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725; Barton and Head, *loc. cit.*) to obtain the rate constants for

the bimolecular additions of hydrogen chloride to the olefins. Thus, if the decomposition rate constant equations are applicable at 200°, the rate constants of the bimolecular additions of hydrogen chloride to ethylene, propene, and *iso*butene are $10^{9\cdot8}$ exp $(-44{,}000/RT)$, $10^{9\cdot0}$ exp $(-34{,}000/RT)$, and $10^{6\cdot1}$ exp$(-25{,}000/RT)$ l. mole^{-1} sec.$^{-1}$ respectively.

Although, under normal experimental conditions, one might expect that these mechanistically bimolecular reactions would be swamped by alternative faster ionic reactions, these rate constants are interesting theoretically. The non-exponential terms fall, as expected, with increase in complexity of the olefin. The activation energies, however, invite theoretical justification. Howlett (Thesis, London, 1948) estimated the first of these activation energies to be 48—50 kcal./mole by the semi-empirical method. Such an estimate of these activation energies cannot, however, account for the variation from one reaction to another because the bond dissociation energies involved do not vary significantly from ethyl chloride to *tert.*-butyl chloride.

The equilibrium constant expressions indicate that all three alkyl halides were examined kinetically under conditions where the equilibrium constants were less than 0·1. Thus even at the lowest temperatures for which rate constants for pyrolysis are quoted, 100 mm. initial pressure of reactant would proceed to more than 99% decomposition, and the rate constants are not in error from this cause.

The heat and entropy changes accompanying hydrochlorination of propene (17,540 cal./mole and −34·60 e.u.) may be taken to apply to the mean temperature, 385° K. ΔS°_{385} has been used in conjunction with the values 68·13 for S°_{385} of propene (Kilpatrick and Pitzer, *J. Res. Nat. Bur. Stand.*, 1946, **37**, 163) and 46·38 for S°_{385} of hydrogen chloride (Linnett, *loc. cit.*) to determine the value 79·91 for S°_{385} of *iso*propyl chloride. This "experimental" value for the entropy may be compared with the statistical figure calculated for the rigid molecule, to obtain an estimate of the potential barrier hindering free rotation of the two methyl groups in *iso*propyl chloride. The usual assumption that translational, rotational, and vibrational contributions may be treated separately was made to calculate the statistical entropy. By assuming the dimensions of the *iso*propyl chloride molecule to be C–H, 1·10; C–C, 1·54; C–Cl, 1·77 Å, and that all interbond angles are tetrahedral, one of the principal momental axes is calculated to be inclined at 15° 34·5′ to the C–Cl bond. The principal moments of inertia are given in Table 4. The vibrational entropy was found by using the frequencies given by Sheppard (*Trans. Faraday Soc.*, 1950, **46**, 533) grouped as follows: 2920 (7), 1461 (2), 1446 (2), 1386, 1372, 1337, 1258, 1160, 1129, 1060, 949, 935, 882, 614, 424, 337, and 326 cm.$^{-1}$ S(trans. + rot. + vib.) at 385° K is thus found to be 73·709, leaving 6·20 e.u. arising from the two internal rotations. With the appropriate reduced moment of inertia (I_m) (see Table 4), reference to Pitzer and Gwinn's tables (*J. Chem. Phys.*, 1942, **10**, 428) indicates that the hindering potential (V) is 2200 cal./mole for each methyl group. This has been used to calculate the entropy of *iso*propyl chloride over the range 298—700° K. The results are collected in Table 5, which also gives the calculated values of the heat of formation (ΔH_f°) and the heat capacity (C_p°) over the same temperature range. In these last computations the effect upon C_p° of estimating the vibrational contributions according to the approximate method suggested by Crawford and Parr (*J. Chem. Phys.*, 1948, **16**, 233), has been compared with Wilson's more exact table of C_p° contributions (cf. Taylor and Glasstone, "Physical Chemistry," Macmillan, London, 1942). Crawford and Parr claimed an overall accuracy of 2% on C_p° for simple molecules. This statement is substantiated in all the cases considered here.

A similar treatment has been carried through for ethyl chloride. Thus ΔS° for hydrochlorination (−31·50) is taken to be appropriate to 473° K. S°_{473} for ethylene is 58·04 (cf. Kilpatrick and Pitzer's calculations corrected by using the more recent vibrational assignment of Arnett and Crawford, *J. Chem. Phys.*, 1950, **18**, 118) whilst S°_{473} for hydrogen chloride is 47·84 (Linnett, *loc. cit.*). Therefore S°_{473} for ethyl chloride is 74·38.

Gordon and Giauque, and also Linnett, have calculated the rotational constants for ethyl chloride, but these have been recalculated here by using the same interatomic dimensions as for *iso*propyl chloride. The principal axis, which is not immediately obvious, is thus found to be inclined at 43° 39·6′ to the C–C bond and the newly calculated moments of inertia are given in Table 4. By using the same vibrational assignment as Gordon and

Giauque, S(trans. + rot. + vib.) at 473° K is found to be 71·227, whence the entropy due to internal rotation in ethyl chloride is 3·15 at this temperature. Pitzer and Gwinn's tables indicate in this case that V is 2900 cal./mole. This enables the thermodynamic functions to be computed for ethyl chloride, and some of the results are included in Table 5.

In Part I an arithmetical slip was made in assessing the statistical entropy of *tert.*-butyl chloride. This calculation has therefore been repeated by using Williams and Gordy's value for the larger moments of inertia of this molecule (*J. Chem. Phys.*, 1950, **18**, 994). Thus $S°_{390}$ for the rigid molecule is recalculated as 77·42 and hence the restricted rotational entropy is 7·78. From this, V is estimated to be 3600 cal./mole per methyl group. The thermodynamic functions for *tert.*-butyl chloride have been determined as for ethyl and *iso*propyl chlorides and are included in Table 5, whilst the moments of inertia are given in Table 4.

The calculated heights of the barriers hindering internal rotation in these molecules are extremely sensitive to changes in the experimental value for ΔS, and furthermore they are obtained after a long chain of argument. They are therefore subject to experimental errors and to errors arising from the assumptions made—notably that the molecular partition function may be exactly factorised into contributions from the separate motions, even including two or more internal rotations. Neglect of such coupling between the internal rotations has been discussed by Pitzer (*J. Chem. Phys.*, 1942, **10**, 605). The energy barriers reported should therefore be taken as a general indication of the consistency of the experimental results and supporting assumptions, rather than as exact indications of their heights, although they are undoubtedly of the correct order of magnitude. The result for ethyl chloride may be compared with the figure 3700 cal./mole obtained by Gordon and Giauque (*J. Amer. Chem. Soc.*, 1948, **70**, 4277).

TABLE 4.

Substance	Principal moments of inertia (10^{-40} g.cm.^{2}) I_A	I_B	I_C	I_m	V (cal./mole)
Ethyl chloride	27·63	151·2	168·1	4·704	2900
*iso*Propyl chloride	103·6	185·2	261·3	5·154	2200
tert.-Butyl chloride	185·0	279·7	279·7	5·221	3600

TABLE 5.

Entropies, specific heats, and heats of formation in the gas phase.

T °K =	298·16	400	500	600	700
Ethyl chloride					
$S°$	66·21	71·10	75·54	79·67	83·54
$C_p°$	15·01	18·40	21·41	23·98	26·15
$C_p°$ *	15·30	18·47	21·22	23·70	25·91
$\Delta H_f°$ (kcal.)	−26·66	−27·69	−28·47	−29·07	−29·52
*iso*Propyl chloride					
$S°$	74·10	80·89	87·03	92·76	98·10
$C_p°$	20·93	25·48	29·59	33·19	36·33
$C_p°$ *	21·33	25·58	29·34	32·81	36·01
$\Delta H_f°$ (kcal.)	−34·56	−35·89	−36·93	−37·71	−38·30
tert.-Butyl chloride					
$S°$	77·04	86·04	94·26	101·9	109·0
$C_p°$	27·30	34·01	39·60	44·23	48·11
$C_p°$ *	27·85	34·05	39·21	43·68	47·65
$\Delta H_f°$ (kcal.)	−42·99	−44·53	−45·62	−46·38	−46·90

* Calculated by using Crawford and Parr's equations.

As more measurements appear upon the heights of internal potential barriers it becomes clearer that V is relatively insensitive to variation in the nature of the passing groups, *i.e.*, whether these are hydrogen, chlorine, or fluorine atoms or methyl groups. Thus V is 2·8 kcal./mole for ethane (Kistiakowsky, Lacher, and Stitt, *J. Chem. Phys.*, 1938, **6**, 407), 3·9 for *iso*butane (Aston, Kennedy, and Schumann, *J. Amer. Chem. Soc.*, 1940, **62**, 2059), 2·7 for 1 : 1 : 1-trichloroethane (Rubin, Levedahl, and Yost, *ibid.*, 1944, **66**, 279), 3·4 for 1 : 1 : 1-trifluoroethane (Russell, Golding, and Yost, *ibid.*, p. 16) and it is only in cases such

as hexachloroethane that appreciably higher results are found (cf. Morino and Iwasaki, *J. Chem. Phys.*, **1949**, **17**, 216). It appears therefore that the origin of these barriers cannot lie in dipole interactions, and hence steric effects and/or quadrupole interactions (Lassettre and Dean, *ibid.*, **1948**, **16**, 157; Oosterhoff, *Discuss. Faraday Soc.*, **1951**, **10**, 79) are the only effects which seem capable of giving such barrier heights.

The heats of reaction found from the temperature dependence of the equilibrium constants may be used to determine the C–Cl bond dissociation energies in the alkyl halides. Unfortunately there are some discrepancies in the published estimates of the heats of formation of the ethyl, *iso*propyl, and *tert.*-butyl radicals, upon which such bond strength estimates must rest. Thus the earlier results obtained by the Polanyi school are some 3 kcal. lower than the figures recommended by Stevenson (*Discuss. Faraday Soc.*, **1951**, **10**, 35). For consistency, the electron-impact results have been used throughout this paper. Stevenson (*J. Amer. Chem. Soc.*, **1943**, **65**, 209) considers that these values refer to 298° K and by combining them with Rossini's thermochemical figures for hydrocarbons (*Chem. Rev.*, **1940**, **27**, 1) and the heats of formation of atoms recommended by Cottrell ("The Strengths of Chemical Bonds," Butterworths, London, **1954**) the C–Cl bond dissociation energies in ethyl, *iso*propyl, and *tert.*-butyl chlorides are found to be respectively 80·1, 80·5, and 78·0 kcal./mole at 298° K. These may be compared with the figures given by Lane, Linnett, and Oswin (*loc. cit.*). It may be noted that the alternative use of Eckstein, Scheraga, and Van Artsdalen's determination of $D(C_4H_9^t\text{–H})$ (*J. Chem. Phys.*, **1954**, **22**, 28) would raise $D(C_4H_9^t\text{–Cl})$ by 1·6 kcal./mole.

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Bedford College, London, N.W.1. [*Received, February 2nd*, 1955.]

Stability Sequence of Five Stereoisomeric Perhydro-1 : 4-dioxophenanthrenes.

By P. A. Robins and James Walker.

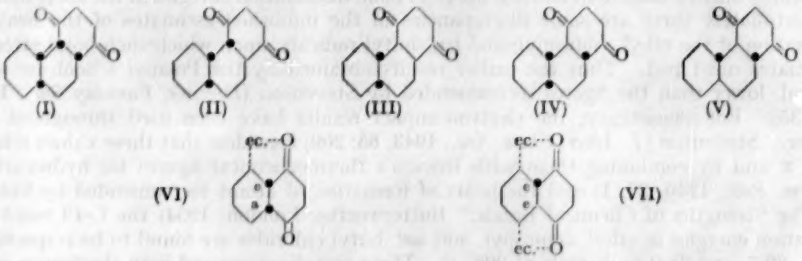
[Reprint Order No. 6122]

A quasi-theoretical stability sequence for five stereoisomeric perhydro-1 : 4-dioxophenanthrenes is shown to agree well with the experimentally established stability sequence if a value of *ca.* 2 kcal./mole is assigned to the energy increment due to the non-bonded interaction between the oxygen atom of a carbonyl group and a β-situated carbon atom in an eclipsed (equatorial) position.

In a previous communication (Robins and Walker, *J.*, **1954**, **3960**) we described the preparation, starting from the stereochemically labile *cis-syn*-$\Delta^{9:14}$-dodecahydro-1 : 4-dioxophenanthrene, of a series of five perhydro-1 : 4-dioxophenanthrenes (I—V). Interconversions by way of characterised intermediates, involving selective methods of reduction and oxidation together with controlled stereochemical inversions at points of ring fusion rendered labile by the presence of adjacent carbonyl groups, enabled a logical assignment of structures to be made to these stereoisomers, and provided experimental evidence for the following stability sequence for the five perhydro-1 : 4-dioxophenanthrenes: *trans-anti-trans* (V) > *trans-syn-cis* (II) > *cis-anti-cis* (III) > *trans-anti-cis* (IV) > *cis-syn-cis* (I). This sequence differs from the stability sequence for the parent perhydrophenanthrenes postulated by Johnson (*Experientia*, **1951**, **7**, 315), namely: *trans-anti-trans* > *trans-syn-cis* = *trans-anti-cis* > *cis-anti-cis* > *cis-syn-cis*, to which that author later (*J. Amer. Chem. Soc.*, **1953**, **75**, **1498**) assigned energy differences as follows: *trans-anti-trans*, 0; *trans-syn-cis* and *trans-anti-cis*, 2·4 kcal./mole; *cis-anti-cis*, 4·0 kcal./mole; and *cis-syn-cis*, *ca.* 6·4 kcal./mole. The reason for the apparently greater *relative* stability of *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (III) as compared with the parent hydrocarbon must be

sought in a factor, or factors, introduced by the carbonyl groups, and it is the object of the present communication to offer an explanation.

When a 1 : 4-dioxo*cyclo*hexane ring is fused with another *cyclo*hexane ring, both being chair forms, a *cis*-fusion (VI) introduces *one* eclipsed configuration (ec.) between the oxygen atom of a carbonyl group and a β-situated equatorial carbon atom contained in the other ring, and a *trans*-fusion (VII) introduces *two* such eclipsed configurations. In this way



it can be seen that the presence of the carbonyl groups has a smaller effect in reducing stability when a 1 : 4-dioxo*cyclo*hexane is fused with a *cyclo*hexane ring in the *cis*-position than when fusion occurs in the *trans*-position, since the greater stability of the *trans*-form of the carbon skeleton is offset by the energy increment for an extra eclipsed O:–C non-bonded interaction. The value of this energy increment can be estimated to be between 1·6 and 2·4 kcal./mole as follows. *trans-anti-trans*-Perhydro-1 : 4-dioxophenanthrene (V) was shown to be completely unaffected by conditions likely to effect its conversion into either *cis-syn-trans*- or *cis-anti-trans*-perhydro-1 : 4-dioxophenanthrene, so that the requisite energy uptake by the carbon skeleton (2·4 kcal./mole) in such a change must exceed the loss due to removal of one O:–C eclipsed non-bonded interaction; this value, 2·4 kcal./mole, may therefore be regarded as the upper limit for the energy increment for an eclipsed O:–C non-bonded interaction. On the other hand *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (IV) was shown to undergo substantial conversion into a mixture of *cis-anti-cis*-(III) and *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (II); (II) and (IV) are of equal energy content both as regards their carbon skeletons and in each having *two* O:–C eclipsed non-bonded interactions, but the formation of (III) from (IV) involves the addition of 1·6 kcal./mole to the energy of the carbon skeleton and the loss of *one* eclipsed O:–C non-bonded interaction, so that a lower limit of 1·6 kcal./mole may be set to the energy increment due to the latter. If we therefore take the energy increment for the O:–C eclipsed non-bonded interaction as 2 kcal./mole we may derive a quasi-theoretical stability sequence for our five stereoisomeric perhydro-1 : 4-dioxophenanthrenes as shown in the Table.

Energy differences of perhydro-1 : 4-dioxophenanthrenes.

	Energy differences due to carbon skeletons * (kcal./mole)	Energy increments on account of eclipsed O:–C non-bonded interaction(s) (kcal./mole)	Net energy differences (kcal./mole)
trans-anti-trans (V)	0	4	0
trans-syn-cis (II) ...	2·4	4	2·4
trans-anti-cis (IV)...	2·4	4	2·4
cis-anti-cis (III) ...	4·0	2	2·0
cis-syn-cis (I).....	*ca.* 6·4	2	*ca.* 4·4

* From Johnson (*J. Amer. Chem. Soc.*, 1953, **75**, 1498).

The " theoretical " order of stability for the five stereoisomeric perhydro-1 : 4-dioxophenanthrenes is therefore now seen to show satisfactory agreement with the experimentally established sequence.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7.

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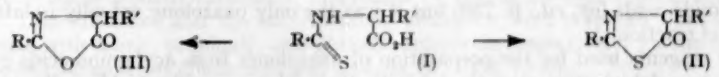
Reactions of α-Thioacylamino-acids. Their Conversion into Thiazolones and Derivatives Thereof.

By J. B. Jepson, Alexander Lawson, and (Miss) V. D. Lawton.

[Reprint Order No. 6126.]

A number of α-amino-acids have been thioacylated by various agents, including thion-esters, then cyclised to thiazolones (II) and under certain conditions acyloxythiazoles (VIII). The thiazolone ring opened readily with amines to give thioacylamino-amides, and condensation with acetone and aromatic aldehydes gave the corresponding alkylidene derivatives. The "orthoformate" synthesis applied to thiohippuric acid gave the oxonols (IX), the heteroalkylidenethiazolones being obtained from sodium thiohippurate and acid anhydrides.

Dehydration of α-acylamino-acids to oxazol-5-ones is a general reaction, the products being useful intermediates in the synthesis of amino-acids and amino-ketones (Carter, "Organic Reactions," Vol. III, p. 198). It seemed of interest to investigate the ring closure of α-thioacylamino-acids (I) which could give thiazol-5-ones (II) by loss of water, or oxazol-5-ones (III) by loss of hydrogen sulphide. A preliminary account of certain aspects of this work was given by McOmie (*Ann. Reports*, 1948, **45**, 207, 209).



The first α-thioacylamino-acid, thiohippuric acid (Gatewood and Johnson, *J. Amer. Chem. Soc.*, 1928, **50**, 2904), was obtained by the action of phosphorus pentasulphide on ethyl hippurate followed by hydrolysis, but in poor yield owing partly to the further formation of alkoxythiazoles (Tarbell, Hirschler, and Carlin, *J. Amer. Chem. Soc.*, 1950, **72**, 3138), and the method sometimes fails (Todd, Bergel, and Karimullah, *J.*, 1936, 1557).

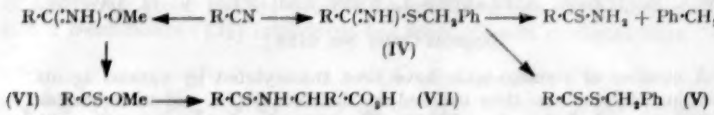
Thioacylation of amines by dithio-acids, developed first by Todd *et al.* (*loc. cit.*) and used by Wuytes and Vaerenburgh (*Bull. Soc. chim. belges*, 1939, **48**, 329), was applied to a number of amino-acids with the use of dithiophenylacetic acid by several groups of workers in the penicillin field ("Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 778). To avoid the earlier difficulties Todd and Topham (Manchester Group, Committee of Penicillin Synthesis, Report No. 93, 1944) and other workers used methyl dithiophenylacetate, purified by distillation, but the supply of such esters was governed by the availability of the acids.

(Thiobenzoylthio)acetic acid ($Ph{\cdot}CS{\cdot}S{\cdot}CH_2{\cdot}CO_2H$), which can be purified by crystallisation, was used by Holmberg (Svedberg Memorial Volume, Uppsala, 1944, p. 299) to thiobenzoylate a number of amino-acids, and later by Kjaer (*Acta Chem. Scand.*, 1950, **4**, 1347; 1952, **6**, 1374) who also used (phenylthioacetylthio)acetic acid (*ibid.*, 1952, **6**, 327). We have found this method satisfactory for the thioacylation of all the amino-acids tried except α-amino*iso*butyric acid for which no method was successful.

Houben and Zivadinovich (*Ber.*, 1936, **59**, 2352) obtained benzyl dithioformate (V; R = H) by the action of hydrogen sulphide on benzyl thioformimidate (IV; R = H). We prepared other benzyl thioimidates (IV; R = Me or CH_2Ph) but no evidence of the formation of the dithioesters (V) was obtained on treatment with hydrogen sulphide; decomposition into the thiol and the thioamide resulted. This parallels the hydrolysis of imidates in that formimidates and aromatic imidates give the corresponding esters whereas aliphatic imidates give the amides (cf. Hartigan and Cloke, *J. Amer. Chem. Soc.*, 1945, **67**, 709; McElvain and Fajardo-Pinzon, *ibid.*, p. 690).

As monothiol esters are powerful acylating agents (Schwyzer, *Helv. Chim. Acta*, 1953, **36**, 414), we considered monothion-esters would be useful thioacylating agents. Methyl thionbenzoate (VI; R = Ph), prepared from methyl benzimidate and hydrogen sulphide

(Sakurada, *Mem. Coll. Sci. Eng. Kyoto*, **1926**, **10**, 67), proved very suitable for the thiobenzoylation of amino-acids. Good yields were obtained with glycine, alanine, phenylalanine, aspartic acid, and glutamic acid, the products being identical with those prepared by the Holmberg method (*loc. cit.*). Although the yields were not so high as in the latter case,



the method is of wider scope and can be applied with aliphatic thion-esters. For example (as reported by Jepson and McOmie, Theses, Oxford, 1946), thiohexanoylglycine (VII; R = C_5H_{11}, R' = H) can be prepared in much higher yield by using methyl thionhexanoate from methyl hexanimidate than by using dithiohexanoic acid (*op. cit.*, p. 710).

Reaction at room temperature of the thioacylamino-acids (VII) with ethanolic silver nitrate gave the oxygen analogues, together with silver sulphide. This constitutes a convenient method for the identification of the thion group (Karjala and McElvain, *J. Amer. Chem. Soc.*, **1933**, **55**, 2966).

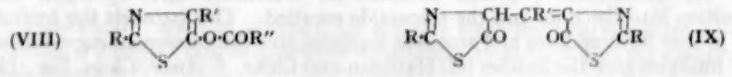
Simultaneous desulphurisation and ring closure of thiohippuric acid (VII; R = Ph, R' = H) by reaction with fresh silver oxide gave 2-phenyloxazol-5-one (III; R = Ph, R' = H) smoothly in 61% yield. Other sulphur-removing agents were less successful. The reaction supports the probability of oxazolone intermediates in the reactions of phenylthioacetamido-acids (*op. cit.*, p. 730) but it was the only oxazolone actually isolated from this type of reaction.

Those reagents used for the preparation of oxazolones from acylamino-acids gave the corresponding dehydrative ring closure with thioacylamino-acids, yielding the thiazol-5-ones (II). For example, acetic anhydride (in the absence of a basic catalyst) gave the free thiazolones, whereas phosphorus tribromide yielded the corresponding hydrobromides from which the free bases could be liberated. Thiobenzoyl-aspartic and -glutamic acid formed thiazolones, in contrast to the oxygen analogues which give anhydrides (Swan, *Nature*, 1952, **169**, 826; Lawson, *J.*, 1953, 1046). Such structures were assigned on the basis of their acid reaction, failure to react rapidly with ethanolic silver nitrate, and the similarity of their ultraviolet absorption spectra to that of other thiazolones (see Table 2) and in contrast to that of benzoylaspartic anhydride ($\lambda_{max.}$ 2300 and 3030 Å; ε 10,230 and 316 in EtOH).

In the presence of traces of pyridine, thioacyl-glycine and -alanine with acyl anhydrides gave acyl derivatives (VIII) of the enolised thiazolones, which were also obtained as their hydrochlorides when the free thiazolones were warmed with acyl chlorides in benzene. Chemical evidence for the structure assigned to these substances was their basicity, their hydrolysis to the original thioacylamino-acids, their failure to react with amines or aldehydes, and the preparation of analogous compounds from glycine and alanine derivatives. The formation of such acyl derivatives under these conditions is in contrast to the behaviour of oxazolones.

The ring-opening reactions of thiazolones were analogous to those of the oxazolones. By reaction with ammonia, amines, and phenylhydrazine the expected derivatives were readily obtained. Thiohydantoins, however, were not formed with ammonium thiocyanate.

2-Phenylthiazol-5-one (II; R = Ph, R' = H) with acetone and aromatic aldehydes, in the absence of an acid anhydride, gave the 4-alkylidene derivatives, also obtained directly



from thiohippuric acid under azlactonising conditions and identical with the products obtained by treating the corresponding oxazolones with thioacids or hydrogen sulphide (*op. cit.*, p. 791; Lurye and Gatsenko, *J. Gen. Chem., U.S.S.R.*, 1952, **22**, 256; Behringer and Jepson, *Chem. Ber.*, 1952, **85**, 138).

The " orthoformate " synthesis used by several groups of workers to prepare 4-heteromethylene-5-oxazolones (*op. cit.*, p. 743) was applied to thioacylamino-acids by Abraham, Baker, Chain, and Robinson (*op. cit.*, p. 847), who from phenylthioacetylglycine and ethyl orthoformate obtained a product to which they assigned the methinoxonol structure (IX; R = CH_2Ph, R′ = H). The same product was later obtained by du Vigneaud (Cornell Group, Committee of Penicillin Synthesis, Report No. 470, 1945) who formulated it as the double anhydride of phenylthioacetylglycine. A homologue of this substance has been prepared by using ethyl orthoacetate, and both thiohippuric acid and 2-phenylthiazol-5-one have been employed to obtain the analogous derivatives (IX; R = Ph) from ethyl orthoformate and other orthoesters. Direct chemical evidence in favour of the methinoxonol structure was provided by the reaction between 4-ethoxyethylidene-2-phenylthiazol-5-one, obtained from thiohippuric acid under modified conditions, and 2-phenylthiazol-5-one which gave the product (IX; R = Ph, R′ = Me) obtainable directly from thiohippuric acid and ethyl orthoacetate. The ready formation of these oxonols, in particular, methinoxonols, shows a further difference in the reactivity of the hydrogen atoms in the 4-position of thiazolones and of oxazolones. The oxonols having a phenyl substituent on the thiazole ring gave intensely blue or red solutions, but the colours were not light-fast enough to make the substances useful as photographic sensitisers.

4-Ethoxyethylidene-2-phenylthiazolone behaved rather differently from the corresponding oxazolone. It reacted as expected with aniline to give the 4-anilinoethylidene-2-phenylthiazolone, but in boiling water the thiazole ring remained intact and the 4-hydroxyethylidene-2-phenylthiazolone, unaffected by boiling 5N-hydrochloric acid, was obtained. This substance and the corresponding analogues were prepared from sodium thiohippurate with acetic, propionic, and phthalic anhydride respectively, by the method used in the oxazolone series (Bullerwell and Lawson, *J.*, 1952, 1350).

Experimental

Benzyl Phenylthioacetimidate.—Dry hydrogen chloride was passed through a solution of equimolar quantities of benzyl cyanide and toluene-ω-thiol in ether at 0°. The *hydrochloride* which crystallised overnight had m. p. 138—142° (decomp.) (from acetone–chloroform) (Found: C, 64·3; H, 5·9; Cl, 13·4. $C_{15}H_{16}NClS$ requires C, 65·0; H, 5·8; Cl, 12·8%). The hydrochloride (5·7 g.) was added slowly to cold aqueous potassium carbonate [3·5 g. (3 equiv.) in 20 ml.], covered with ether, and shaken till dissolved. Removal of the ether gave *benzyl phenylthioacetimidate* (4·4 g., 89%), m. p. 47—48° (decomp.), colourless plates from ethanol (Found: C, 74·5; H, 6·3. $C_{15}H_{15}NS$ requires C, 74·7; H, 6·2%). Decomposition into benzyl cyanide and toluene-ω-thiol took place slowly on storage and very rapidly with alkali. Passing hydrogen sulphide into an ethereal solution of the phenylthioacetimidate gave toluene-ω-thiol (80%) and phenylthioacetamide (64%). Similarly benzyl thioacetimidate (m. p. of hydrochloride was 156°; Houben *et al.*, *loc. cit.*, gave 153°) by reaction with hydrogen sulphide gave toluene-ω-thiol (91%) and thioacetamide (81%).

Methyl Hexanimidate Hydrochloride.—*n*-Hexanonitrile and methanol similarly gave this *hydrochloride* (90%), m. p. 91° (plates from dioxan–ether) (Found: N, 8·3; Cl, 22·1. $C_7H_{16}ONCl$ requires N, 8·4; Cl, 21·5%). The free *imidate*, a colourless oil with a characteristic odour, b. p. 60—62°/18 mm., was liberated from the hydrochloride by 5N-sodium hydroxide and extracted with ether (80%) (Found: C, 65·4; H, 11·7; N, 10·7. $C_7H_{15}ON$ requires C, 65·2; H, 11·6; N, 10·8%).

Thiohexanoylglycine.—Dry hydrogen sulphide was passed through a cooled dry ethereal solution of the imidate until precipitation of the ammonium sulphide was complete. After removal of the precipitate by treatment with water, the yellow ether solution containing the thionester was shaken with a solution of glycine in 3N-sodium hydroxide for 18 hr. Acidification of the aqueous layer with concentrated hydrochloric acid at 0°, followed by ether-extraction, gave thiohexanoylglycine, m. p. 108° (white plates from water), in 40% overall yield from the nitrile. Identical material was obtained by using dithiohexanoic acid but the maximum yield was only 3·5% from pentyl bromide.

Methyl Thionbenzoate.—Dry hydrogen sulphide was passed through a solution of methyl benzimidate, b. p. 106°/24 mm. (25 g.), in ether (25 ml.) at 0°. After 1 hr. the yellow solution was shaken with water to remove ammonium sulphide, and the ether layer was dried ($MgSO_4$)

and again treated with hydrogen sulphide for a further 2 hr. After being shaken with water the ether layer was quickly separated, then dried, and the ether removed. The yellow methyl thionbenzoate (81%) distilled at 112—116°/21 mm., leaving a residue of thiobenzamide.

Thiobenzoylation of Amino-acids.—Methyl thionbenzoate (8·2 g., 0·05 mol.) in ether (25 ml.) was vigorously shaken for 18 hr. with a solution of the amino-acid (0·055 mol.) in 3N-sodium hydroxide (30 ml.). The yellow aqueous layer was separated and acidified with concentrated hydrochloric acid at 0°. By this method (A) the yield of thiohippuric acid was 73%, against 37% by Gatewood and Johnson's method (*loc. cit.*) (B) and 78% by Holmberg's method (*loc. cit.*) (C). The new thiobenzamido-acids prepared are shown in Table 1.

TABLE 1. *Thiobenzamido-acids*, Ph·CS·NH·CHR'·CO_2H.

Amino-acid	R'	Method	Yield (%)	M. p.[a]	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
DL-Aspartic acid ...	$CH_2·CO_2H$	A	52	162°	$C_{11}H_{11}O_4NS$	52·1	4·5	52·2	4·3
" ...	"	C	79	"	"	—	—	—	—
DL-Glutamic acid ...	$[CH_2]_2·CO_2H$	A	47	159	$C_{12}H_{13}O_4NS$	54·1	5·0	53·9	4·9
" ...	"	C	76	"	"	—	—	—	—
DL-Valine	Pr^i	C	73	90	$C_{12}H_{15}O_2NS$	60·9	6·1	60·8	6·3
DL-Norleucine	Bu^n	C	72	142	$C_{13}H_{17}O_2NS$	61·9	6·6	62·2	6·8
DL-Phenylacetic acid	Ph	C	80	145	$C_{15}H_{13}O_2NS$	66·2	4·7	66·4	4·8
DL-Phenylalanine ...	CH_2Ph	A	70	115	$C_{16}H_{15}O_2NS$	67·0	5·1	67·4	5·3
" ...	"	C	78	"	"	—	—	—	—
DL-Tyrosine	$CH_2·C_6H_4·OH$	C	40	108[b]	$C_{16}H_{15}O_3NS$	63·4	4·8	63·8	5·0
DL-Serine	$CH_2·OH$	C	83	139[c]	$C_{10}H_{11}O_3NS$	53·6	4·9	53·3	4·9
DL-Methionine	$CH_2·CH_2·SMe$	C	75	95[c]	$C_{12}H_{15}O_2NS_2$	53·5	5·6	53·5	5·6

[a] Solvent: ethyl acetate, except as stated. [b] From water. [c] From benzene.

2-Phenyloxazol-5-one.—Thiohippuric acid (2·0 g.) and fresh silver oxide (7·8 g.) were shaken together in dry ether (70 ml.) for 40 hr. The red ethereal solution was centrifuged and evaporated to give the oxazolone, m. p. 86° (1 g., 61%), as pink prisms from ethanol. The use of silver benzenesulphonate in chloroform solution at 0° instead of silver oxide in this reaction gave an inferior yield.

2-Phenylthiazol-5-one.—A solution of thiohippuric acid (2 g.) in acetic anhydride (25 ml.) was heated on the steam-bath for 1 hr. and evaporated under reduced pressure. The residue was extracted with boiling light petroleum (b. p. 40—60°) from which the *thiazolone* crystallised on cooling. Repeated crystallisation from light petroleum gave colourless plates, m. p. 84° (Found: C, 61·3; H, 4·0; N, 7·7; S, 18·0. C_9H_7ONS requires C, 61·1; H, 4·0; N, 7·9; S, 18·1%). *2-Phenylthiazol-5-one hydrochloride*, obtained by passing anhydrous hydrogen chloride into an ether solution of the base, had m. p. 149° (needles from ethyl acetate) (Found: C, 50·7; H, 3·4. C_9H_8ONSCl requires C, 50·6; H, 3·3%); light absorption: $\lambda_{max.}$ 2950 Å, ε 10,470 in EtOH. The *picrate* (needles from ethyl acetate) had m. p. 122° (Found: C, 45·0; H, 2·6. $C_{15}H_{10}O_8N_4S$ requires C, 44·3; H, 2·5%). 2-Phenylthiazol-5-one was also obtained by treating thiohippuric acid with phosphorus trichloride or tribromide in dry dioxan or ether and shaking a suspension of the precipitated salt in ether with sodium acetate. The other thiazolones shown in Table 2, except for the aspartic and glutamic acid derivatives, were prepared from the corresponding thioacylamino-acids by using acetic anhydride as for 2-phenylthiazolone above. Their picrates are described in Table 3. Thiobenzoylaspartic and glutamic acid were converted into

TABLE 2. *Thiazol-5-ones* (II).

Parent amino-acid	R	R'	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H	Light absorption in EtOH $\lambda_{max.}$ (Å)	Light absorption in EtOH ε
Alanine	Ph	Me	96°[a,d]	$C_{10}H_9ONS$	62·5	4·7	62·8	4·7	3050	9120
Valine	Ph	Pr^i	69[b,e]	$C_{12}H_{13}ONS$	65·1	5·8	65·8	5·9	—	—
Leucine	Ph	Bu^i	41[a,e]	$C_{13}H_{15}ONS$	66·3	6·3	66·9	6·4	—	—
Phenylalanine	Ph	CH_2Ph	72—73[a,e]	$C_{16}H_{13}ONS$[g]	71·5	4·7	71·9	4·9	3050	14,450
Aspartic acid	Ph	$CH_2·CO_2H$	154[c,f]	$C_{11}H_9O_3NS$	55·9	3·9	56·2	3·8	3050	12,300
Glutamic acid	Ph	$[CH_2]_2·CO_2H$	152[c,f]	$C_{12}H_{11}O_3NS$	58·1	4·7	57·8	4·4	3050	12,880
Glycine	$Ph·CH_2$	H	45[b,e]	$C_{10}H_9ONS$	62·1	5·0	62·8	4·7	—	—
Alanine	$Ph·CH_2$	Me	87[a,e]	$C_{11}H_{11}ONS$	64·0	5·2	64·4	5·4	—	—

[a] Needles. [b] Plates. [c] Prisms. [d] From ethyl acetate. [e] From light petroleum. [f] From benzene. [g] Lurye and Gatsenko (*loc. cit.*) give m. p. 112° for a compound claimed to have this structure.

the thiazolones by dissolving them in warm acetic anhydride, adding benzene, and cooling. They did not form picrates. Other thiazolones were not purified (see footnote, Table 4).

TABLE 3. *Picrates of thiazolones* (II).

R	R′	Form, solvent	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Ph	Me	Needles, EtOAc	154°	$C_{16}H_{13}O_8N_4S$	45·2	3·0	45·4	2·9
Ph	Pr^i	Prisms, EtOH	117	$C_{18}H_{16}O_8N_4S$	48·6	3·8	48·2	3·6
Ph	Bu^t	Needles, EtOH	98	$C_{19}H_{18}O_8N_4S$	50·0	4·25	49·35	3·9
Ph	Ph·CH$_2$	Needles, EtOH	123	$C_{22}H_{16}O_8N_4S$	53·2	3·4	53·2	3·2
Ph·CH$_2$	H	Needles, EtOH	106	$C_{16}H_{13}O_8N_4S$	45·9	2·8	45·4	2·9
Ph·CH$_2$	Me	Needles, EtOH	144	$C_{17}H_{14}O_8N_4S$	47·5	3·4	47·0	3·2

2-Phenyl-4 : 5-benzo-1 : 3-thiazin-6-one.—(Thiobenzoyl)anthranilic acid (2 g.) was dissolved in warm acetic anhydride (10 ml.). On cooling, the *thiazinone* crystallised. It had m. p. 113° (felted needles from light petroleum) (Found : C, 71·0; H, 3·7. $C_{14}H_9ONS$ requires C, 70·3; H, 3·8%). Light absorption : $\lambda_{max.}$ 2500, 2950, and 3450 Å, ε 30,200, 11,200, and 9120 in EtOH.

Thioacylaminoamides (*Table* 4).—These were prepared by boiling the thiazolones in toluene with the appropriate amine for a few minutes and cooling. The thiazolones and ammonia in boiling dioxan gave the thioacylamino-acid amides identical with those prepared by Kjaer (*loc. cit.*).

TABLE 4. *Thioacylamino-acid derivatives.*

	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Thiobenzoylglycine anilide	152° [a]	$C_{15}H_{14}ON_2S$	66·5	5·4	66·7	5·2
Thiobenzoylglycine morpholide	158 [b]	$C_{13}H_{16}O_2N_2S$	58·9	6·3	59·1	6·1
Thiobenzoylglycine phenylhydrazide ...	190 [b]	$C_{15}H_{14}ON_2S$	63·4	5·3	63·2	5·3
Phenyl(thioacetyl)glycine anilide	165 [a]	$C_{15}H_{14}ON_2S$	67·7	5·7	67·6	5·6
Phenyl(thioacetyl)glycine benzylamide	130 [a]	$C_{17}H_{18}ON_2S$	68·3	6·1	68·5	6·1
Thiobenzoyl-DL-alanine anilide	155 [a]	$C_{16}H_{16}ON_2S$	67·2	5·8	67·6	5·6
Phenyl(thioacetyl)-DL-alanine anilide...	159 [a]	$C_{17}H_{18}ON_2S$	68·7	5·9	68·5	6·1
Thiobenzoyl-DL-valine anilide	215 [a]	$C_{18}H_{20}ON_2S$	69·15	6·4	69·2	6·4
Thiobenzoyl-DL-leucine anilide	164 [a]	$C_{19}H_{22}ON_2S$	69·5	6·6	70·0	6·75
Thiobenzoyl-DL-norleucine anilide [c] ...	165 [b]	$C_{19}H_{22}ON_2S$	69·7	6·7	70·0	6·75
Phenyl(thioacetyl)-DL-leucine anilide [c]	170 [b]	$C_{20}H_{24}ON_2S$	70·0	7·4	70·6	7·6
Thiobenzoyl-DL-phenylalanine anilide	176—177 [a]	$C_{22}H_{20}ON_2S$	73·0	5·7	73·3	5·6
Thiohexanoylglycine anilide [c].....	113 [a]	$C_{14}H_{20}ON_2S$	63·4	7·4	63·6	7·6

[a] From aqueous ethanol. [b] From ethanol. [c] The crude thiazolones were made to react directly with aniline.

4-Benzylidene-2-phenylthiazol-5-one.—2-Phenylthiazolone (1·7 g.) was dissolved in ethanol (5 ml.), and benzaldehyde (1 ml.) and pyridine (1 drop) were added. After 30 min. on the steam-bath the thiazolone was collected and crystallised from ethanol (yield 1·8 g.); it had m. p. 130° and $\lambda_{max.}$ 3800 and 2900 Å, ε 22,400 and 15,850 in EtOH. The thiazolone heated for 3 hr. in benzene with aniline and a crystal of aniline hydrochloride gave an 89% yield of *thiobenzamidocinnamic anilide*, m. p. 149° (needles from ethanol) (Found : C, 73·2; H, 5·0. $C_{22}H_{18}ON_2S$ requires C, 73·7; H, 5·0%).

4-4′-Methylbenzylidene-2-phenylthiazol-5-one.—This *compound*, prepared as above from 2-phenylthiazolone and *p*-tolualdehyde, crystallised from ethanol in red silky needles, m. p. 121° (yield 68%) (Found : C, 72·7; H, 4·7. $C_{19}H_{13}ONS$ requires C, 73·0; H, 4·7%).

4-(2 : 3-Dimethoxybenzylidene)-2-phenylthiazol-5-one.—This *compound*, prepared as above, crystallised from ethanol in yellow needles, m. p. 127° (70%) (Found : C, 66·4; H, 4·7. $C_{18}H_{15}O_3NS$ requires C, 66·0; H, 4·7%).

2-Phenyl-4-isopropylidenethiazol-5-one.—2-Phenylthiazolone (1·5 g.), anhydrous sodium acetate (0·75 g.), and dry acetone (25 ml.) were heated under reflux with a few drops of pyridine for 15 hr. The solution was then poured on crushed ice, and the bulky precipitate crystallised from ethanol. It had m. p. 99° (yield 54%) and was identical with the substance prepared from phenyl*iso*propylideneoxazolone (*op. cit.*, p. 791).

5-Acetoxy-2-phenylthiazole.—Method A. Thiohippuric acid (4 g.) was heated in acetic anhydride (20 ml.) containing pyridine (5 drops) on the steam-bath for 1 hr. The red oil remaining after removal of the excess of acetic anhydride *in vacuo* crystallised from ethanol to give the *thiazole*, colourless needles, m. p. 59° (88%) (Found : C, 60·5; H, 4·4; N, 6·2; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1; N, 6·4; S, 14·6%).

Method B. 2-Phenylthiazolone was warmed with excess of acetyl chloride in benzene. The

precipitated thiazole hydrochloride was collected and triturated with 3N-sodium hydroxide under ether. The dried ether layer on evaporation gave the thiazole. The *picrate* crystallised from ethanol in needles, m. p. 125° (Found : C, 45·8; H, 2·8. $C_{17}H_{12}O_9N_4S$ requires C, 45·5; H, 2·7%).

5-Acetoxy-2-benzylthiazole.—The thiazole was prepared from 2-benzylthiazolone as above. It did not crystallise but gave a *picrate*, needles (from ethanol), m. p. 147° (Found : C, 47·4; H, 2·9. $C_{18}H_{14}O_9N_4S$ requires C, 47·8; H, 3·0%).

5-Acetoxy-4-methyl-2-phenylthiazole.—The *thiazole*, prepared from 4-methyl-2-phenylthiazolone as above, crystallised from ethanol in colourless needles, m. p. 110° (Found : C, 61·6; H, 4·7. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%). The *picrate*, needles from ethanol, had m. p. 155° (Found : C, 47·5; H, 2·7. $C_{18}H_{14}O_9N_4S$ requires C, 47·8; H, 3·0%).

5-Acetoxy-2-benzyl-4-methylthiazole.—The *thiazole*, prepared by the above method, b. p. 140°/0·1 mm., solidified to colourless plates, m. p. 33° (Found : C, 63·1; H, 5·4. $C_{13}H_{13}O_2NS$ requires C, 63·2; H, 5·3%). It gave a labile *monohydrate*, m. p. 46° (Found : C, 59·3; H, 5·7. $C_{13}H_{13}O_2NS,H_2O$ requires C, 59·0; H, 5·7%), and a *picrate*, rhombs (from ethanol), m. p. 108° (Found : C, 47·8; H, 3·0. $C_{19}H_{16}O_9N_4S$ requires C, 48·0; H, 3·4%).

5-Benzoyloxy-2-phenylthiazole.—The *thiazole*, prepared by method *B* (above), using benzoyl chloride, crystallised from ethanol in pale brown needles, m. p. 129° (Found : C, 68·2; H, 3·8. $C_{16}H_{11}O_2NS$ requires C, 68·4; H, 3·9%). The *picrate*, plates from ethanol, had m. p. 162—163° (Found : C, 52·2; H, 2·6. $C_{22}H_{14}O_9N_4S$ requires C, 51·8; H, 2·8%).

4-Ethoxyethylidene-2-phenylthiazol-5-one.—Thiohippuric acid (3·2 g.) was heated with ethyl orthoacetate (3 ml.) and acetic anhydride (3 ml.) in xylene (150 ml.) on the steam-bath for 1 hr. Removal of the solvents *in vacuo* left a red oil which was repeatedly extracted with hot light petroleum from which (after decolorisation with charcoal) the *thiazolone* (1 g.) crystallised in colourless needles, m. p. 96° (Found : C, 62·5; H, 5·5; N, 5·4. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; N, 5·7%).

4-Hydroxyethylidene-2-phenylthiazol-5-one.—Method A. The 4-ethoxy-derivative (above) (1 g.) was boiled with water (10 ml.) for 15 min. The oily *thiazolone* which crystallised on cooling crystallised from water as yellow needles (0·5 g.), m. p. 129° (Found : C, 60·6; H, 4·2. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1%). Light absorption : $\lambda_{max.}$ 3400 and 2600 Å, ε 28,200 and 19,950 in EtOH.

Method B. Sodium thiohippurate (4·3 g.), 2-picoline (6 ml.), and acetic anhydride (6 ml.) were heated on the steam-bath for 30 min. Ethanol (4 ml.) was added to remove acetic anhydride, and the solution was poured into water (30 ml.) which was then acidified with 5N-hydrochloric acid (20 ml.). The brown precipitate of the thiazolone was crystallised as above (yield 3 g.). *4-Anilinoethylidene-2-phenylthiazol-5-one* was prepared by treating the ethoxyethylidenethiazolone with aniline at room temperature and crystallising the product from ethanol from which it was obtained as yellow needles, m. p. 138° (Found : C, 69·1; H, 4·9. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8%).

4-Hydroxypropylidene-2-phenylthiazol-5-one.—This *compound*, obtained as above (method B) by using propionic anhydride, formed yellow needles, m. p. 84° (Found : C, 61·7; H, 4·4. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%).

2-Phenyl-4-phthalidylidenethiazol-5-one.—Sodium thiohippurate (2 g.), acetic anhydride (4 ml.), and phthalic anhydride were heated on the steam-bath for 1·5 hr. The solid *product* was washed with ethanol and recrystallised from toluene as orange prisms, m. p. 274° (Found : C, 66·5; H, 2·9; N, 4·3. $C_{17}H_9O_3NS$ requires C, 66·6; H, 2·9; N, 4·6%).

Reaction between Thioacylamino-acids and Orthoesters.—Thiohippuric acid (3·2 g.), ethyl orthoformate (2·8 ml.), and acetic anhydride (3 ml.) were heated under reflux on an oil-bath. After 10 min. the solid mass was washed with ethanol and recrystallised from toluene–ethyl acetate, to give *di-(2-phenyl-4-thiazol-5-one)methinoxonol* (IX; R = Ph, R′ = H) (2·5 g.), dark brown needles, m. p. 245° (decomp.) (Found : C, 61·9; H, 3·7. $C_{19}H_{12}O_2N_2S_2$ requires C, 62·6; H, 3·3%). Light absorption $\lambda_{max.}$ 5350 and 2900 Å, ε 28,200 and 22,400 in $CHCl_3$.

Di-(2-p-nitrophenyl-4-thiazol-5-one)methinoxonol, black needles, m. p. 286° (decomp.), was obtained by the same method from *N*-4-nitrobenzoylglycine (Found : C, 50·3; H, 2·5. $C_{19}H_{10}O_6N_4S_2$ requires C, 50·2; H, 2·2%). Light absorption : $\lambda_{max.}$ 5800 and 3000 Å, ε 35,500 and 19,900 in $CHCl_3$.

Methyldi-(2-phenyl-4-thiazol-5-one)methinoxonol (IX; R = Ph, R′ = Me) was obtained as above by using ethyl orthoacetate, as brown needles (from toluene), m. p. 284° (decomp.) (Found : C, 62·7; H, 4·0%; *M*, 393. $C_{20}H_{14}O_2N_2S_2$ requires C, 63·4; H, 3·7%; *M*, 378). Light absorption : $\lambda_{max.}$ 5300 and 2860 Å, ε 25,100 and 22,900 in $CHCl_3$. The same substance was

obtained by refluxing a solution in toluene of equimolecular amounts of 2-phenylthiazol-5-one and 4-ethoxyethylidene-2-phenylthiazol-5-one with a few drops of acetic anhydride or triethylamine.

Methyldi-(2-benzyl-4-thiazol-5-one)methinoxonol (IX; R = CH_2Ph, R′ = Me) was obtained from phenylthioacetylglycine (2·1 g.) and ethyl orthoacetate (1·8 ml.) at the b. p. with acetic anhydride (1·9 ml.) for 2 hr. The product (1·0 g.) crystallised from ethyl acetate in red rhombs, m. p. 170° (decomp.) (Found: C, 64·7; H, 4·2%; *M*, 420. $C_{22}H_{18}O_2N_2S_2$ requires C, 65·0; H, 4·4%; *M*, 406). Light absorption: $\lambda_{max.}$ 4550 and 3800 Å, ε 26,300 and 5010 in EtOH.

Ethyldi-(2-phenyl-4-thiazol-5-one)methinoxonol (IX; R = Ph, R′ = Et) was obtained as above by using ethyl orthopropionate, as red lustrous needles (from toluene), m. p. 246° (decomp.) (50%) (Found: C, 64·1; H, 4·2%; *M*, 400. $C_{21}H_{16}O_2N_2S_2$ requires C, 64·3; H, 4·1%; *M*, 392). Light absorption: $\lambda_{max.}$ 5200 and 2800 Å, ε 17,780 and 13,180 in EtOH.

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Royal Free Hospital School of Medicine,
8, Hunter Street, London, W.C.1.
Courtauld Institute of Biochemistry,
Middlesex Hospital Medical School, London, W.1. [*Received, February 12th*, 1955.]

Reactions between Solids. Part II. The Reaction between Potassium Perchlorate, Potassium Iodate, and Different Forms of Carbon.*

By Eliahu Hoffmann and Saul Patai.

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The influence of various physical factors such as wetting, pressure in preparation, ageing of tablets, particle size of components, temperature of reaction, and relative quantities of reactants was investigated in the solid–solid reaction of potassium perchlorate and potassium iodate with different forms of carbon. A new empirical rate equation $dx/dt = k(a - x)^{2/3}/x^{1/3}$ is proposed and it is shown to be valid for a wide range of different stoicheiometrical mixtures. Factors influencing the reaction rate are discussed.

In Part I * the reaction between solid potassium perchlorate and carbon black was studied with varying initial amounts of the reactants, in the temperature range of 320—385° C. The aim of the present paper was to determine the influence of various physical factors involved on the course of this reaction, using different forms of carbon (Nuchar and sugar charcoal) and also, for comparison, with potassium iodate as the oxidant in some cases.

Experimental.

The apparatus and the experimental procedure have been described elsewhere (Patai, *Experientia*, 1952, **8**, 76).

Preparation of Standard Samples.—Pure potassium perchlorate (Baker's Analysed) of determined particle size was prepared by using American Bureau of Standards sieves. The potassium iodate (Baker's Analysed) was ground to pass a 200-mesh B. of S. sieve. The Nuchar (Eastman Kodak Co.) had an average particle diameter of 0·01 mm. and left, on ignition, 3·5% of residue, of which 0·45% was iron oxide, 0·5% silicon dioxide, and the balance calcium sulphate. The average diameter of the particles of sugar charcoal was 0·02 mm. and the residue of 0·86% which was left on ignition consisted of magnesium and calcium sulphates. It also contained some very strongly absorbed or possibly chemically bound water, which was eliminated at 500° *in vacuo*.

The reactants were thoroughly mixed in various stoicheiometric proportions (the total mixture weighing about 1 g.), wetted with three drops of distilled water, pressed into tablets under a pressure of 2250 kg./cm.^{2} and dried at 120° for 4 hr. Samples of about 50 mg. taken from these tablets were used for the experiments. Each curve shown in the Figures represents

* Part I, Patai and Hoffmann, *J. Amer. Chem. Soc.*, 1950, **72**, 5098.

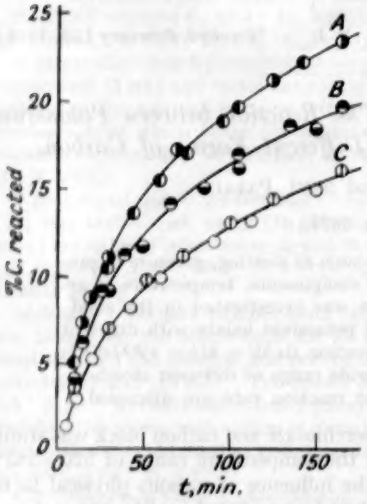
at least two or three runs made under identical conditions. The average experimental error was 1—2%.

Influence of Wetting.—Samples prepared without the addition of water were mechanically weaker and tended to disintegrate on handling. Reaction rates obtained with such samples were constantly lower than those obtained with standard samples. The difference between values obtained after 2—4 hours' reaction time (10—15% reaction) amounted to 2—4% (*i.e.*, a relative difference of 20—25%).

Influence of the Pressure of Preparation of the Samples.—Tablets prepared under a pressure of 1125 kg./cm.^{2} showed lower reaction rates than those prepared under standard conditions (2250 kg./cm.^{2}), differing from the latter by about the same amount as the unwetted from the wetted samples.

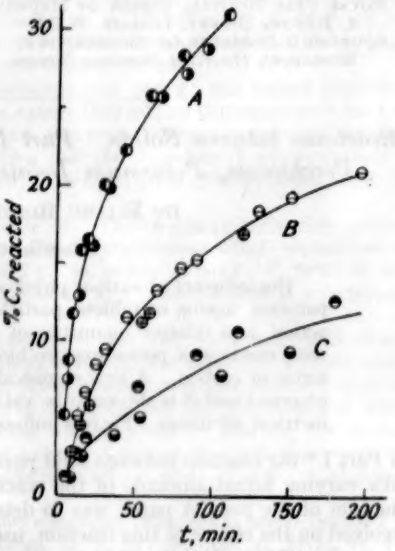
Ageing.—After 14 days' storage of the samples the reaction rates diminished slowly, reaching

FIG. 1. *Influence of the size of the potassium perchlorate particles on the reaction of* 1 *atomic equiv. of Nuchar with* 0·5 *mol. of potassium perchlorate, at* 343°.



A, 200—230; *B*, 170—220; *C*, 140—170 mesh.

FIG. 2. *Influence of the temperature on the reaction of* 1 *atomic equiv. of Nuchar with* 0·5 *mol. of potassium perchlorate* (200—230 *mesh*).



A, 367; *B*, 343; *C*, 319°.

the values characteristic of the unwetted samples after 6—9 months. Aged samples were also more brittle and tended to disintegrate spontaneously.

Influence of Particle Size.—Curves *A*, *B*, and *C* in Fig. 1 show the reaction rates, at 343°, of standard samples prepared with Nuchar and potassium perchlorate of different particle sizes (average diameters, 0·068, 0·081, and 0·0965 mm.). Each curve represents an average of four runs, with the experimental points of two runs only shown for each curve.

Experiments at Different Temperatures.—Fig. 2 shows the reaction rates of standard samples from Nuchar and potassium perchlorate of 200—230 mesh, at 367°, 343°, and 319°.

Experiments with Different Relative Amounts of the Reactants.—(a) *Experiments with potassium perchlorate.* Fig. 3 shows the rates of the reaction of potassium perchlorate in mixtures of 1 atomic equiv. of Nuchar with 2, 1, 0·5, and 0·25 mols. of perchlorate (200—230 mesh), at 343°. Similar curves were also obtained by measuring the rates of the reaction, at 367°, of 1 atomic equiv. of sugar charcoal with 2, 1, 0·5, and 0·25 mols. of potassium perchlorate, respectively.

(b) *Experiments with potassium iodate.* The reaction rates were measured, at 379°, of 1 atomic equiv. of sugar charcoal with 4/3, 2/3, and 1/3 mols. of <200 mesh potassium iodate. The curves obtained were again of the type shown in the previous Figures.

In all these oxidations carbon dioxide was the only gaseous product found. This was shown both by direct analysis of the gas evolved and by comparison of the weight loss of the sample with the weight loss calculated from the volume of the gas produced, the latter being assumed to be pure carbon dioxide.

Discussion.

Physical factors are known to influence solid–solid reactions, but the nature of this influence has rarely been determined. Different crystalline forms of a reactant show different reactivities owing to their different energy contents and surface areas; thus amorphous seem to be generally more reactive that crystalline modifications. It is, therefore, clear that even the mode of preparation of the samples influences the reaction rates (Hedvall, *Z. angew. Chem.*, 1931, **44**, 781). The reaction of potassium perchlorate in our case takes place at temperatures above its transition point (299°), at which a change from a rhombic to a face-centered cubic lattice occurs (Vorlander and Kaascht, *Ber.*, 1923, **56**, 1157). Such lattice changes enhance the reactivity of solid substances (Hedvall, *Z. phys. Chem.*, 1926, **123**, 33).

The variations in the reaction rates of stoicheiometrically identical samples, due to different physical factors such as pressure of preparation, wetting, ageing, and particle size, will mainly be caused by variation in the contact area of the reactants. In the case of ageing there may also be a very slow reaction at room temperature. Even if the occurrence of such a reaction could not be proved by ordinary analytical means, only an extremely thin layer of potassium chloride at the interfaces of the carbon and the potassium perchlorate may be necessary in order to block, at least partially, the reactive spots. The residual moisture left in the samples after drying may also lower the reaction rate, because it may permit the small particles of potassium perchlorate to recrystallise and form larger aggregates. (These traces of moisture are eliminated from the samples only by repeated degassing *in vacuo* at 250°.)

In any case, the influence of the particle size on the reaction rate, as shown in Fig. 1, proves that the rate depends primarily upon the available surface areas. However, the relation between surface area and reaction rate does not seem to be simple. Similar solid–solid heterogeneous systems have been investigated, *e.g.*, by Tammann and by Jander (Tammann, *Z. anorg. Chem.*, 1926, **149**, 21; Jander, *ibid.*, 1927, **163**, 1; 1927, **166**, 31; 1927, **168**, 113). These authors based their treatment of the solid–solid reaction rates on considerations of diffusion processes. During most solid–solid reactions a product layer is formed which separates the reactants and thus the continuation of the process depends on the diffusion of at least one of the reactants through this layer. According to Tammann (*ibid.*, 1920, **111**, 78) the rate of growth of the product layer is $dy/dt = k/y$ (Eq. 1*a*), where y is the thickness of the product layer; the integrated form of this equation is $y^2 = 2kt$ (Eq. 1*b*).

Assuming the rate of growth of the product layer to be proportional to the reaction rate, Jander applied equation 1*b* to the reaction of powder mixtures with one of the reactants in great excess over, and of much smaller particle size than, the second component. Jander has shown that for these cases the following relation applies:

$$y = r\{1 - \sqrt[3]{[(100 - x)/100]}\} \quad \text{(Eq. 2)}$$

where y is again the thickness of the product layer, r is the radius of the original particle, and x is the amount of the product at time t. Substitution of the value of y from Eq. 2 into Eq. 1*b* gives

$$\{1 - \sqrt[3]{[(100 - x)/100]}\}^2 = 2kt/r^2 \quad \text{(Eq. 3)}$$

which was shown by Jander to be correct for various solid–solid reactions in which a homogeneous product layer is formed.

In our case, the amount of the solid product, *i.e.*, the amount of the potassium chloride formed, can be calculated directly and continuously from the amount of carbon dioxide evolved in accordance with the equation $KClO_4 + 2C \longrightarrow KCl + 2CO_2$, and the carbon can be taken, at least in most of our experiments, as the component present in excess,

owing to the much smaller size of its particles. Indeed, in good accord with Eq. 3, a plot of the left-hand side of Eq. 3 as a function of the time gives straight lines. The values of the rate coefficients k for stoicheiometrically identical mixtures of carbon (Nuchar) with

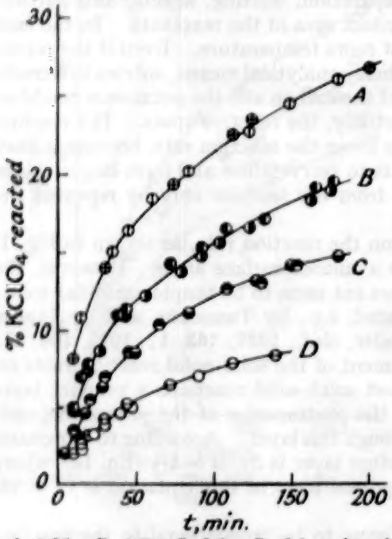
TABLE 1. *Values of the rate coefficients for the reaction of* 1·0 *atomic equiv. of Nuchar with* 0·5 *mol. of potassium perchlorate of different particle sizes, at* 343° (*from Fig.* 1).

Initial average radius of perchlorate particles (mm.)	Initial ratio of the carbon/perchlorate surface area	$10^{10}k$ (cm.^{3} min.$^{-1}$)
0·0483	2120/171	2·25
0·0405	2120/203·7	2·50
0·034	2120/242·6	2·67

potassium perchlorate of three different particle sizes, calculated from the slopes of these lines, after consideration of the factor $2/r^2$, are given in Table 1.

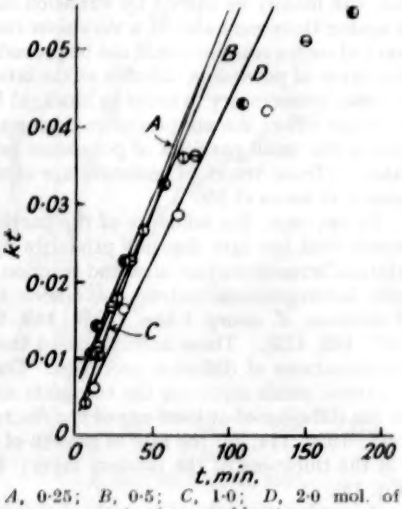
The consistency of the k values appears to be satisfactory when consideration is given to the difficulties of preparing standard mixtures. However, the above equation fails

FIG. 3. *Reaction of different amounts of potassium perchlorate with* 1 *atomic equiv. of Nuchar, at* 343°.



A, 0·25; *B*, 0·5; *C*, 1·0; *D*, 2·0 mols. of perchlorate.

FIG. 4. *Values of kt–t (from equation* 6), *calculated from the experimental runs shown in Fig.* 3.



A, 0·25; *B*, 0·5; *C*, 1·0; *D*, 2·0 mol. of potassium perchlorate.

to explain the fact that reaction rates vary with the initial ratio of the reactants as shown in, *e.g.*, Fig. 3. As in all these mixtures the surface area of the carbon was very much larger than that of the perchlorate particles, there should be practically no variation in the reaction rate, at least not initially. The following empirical rate equation was found to give fairly uniform rate coefficients for stoicheiometrically different mixtures of potassium perchlorate and carbon :

$$dx/dt = k(a - x)^{2/3}/x^{1/3} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(Eq. 4)}$$

Here dx/dt is the rate at which potassium chloride is produced, *i.e.*, at which potassium perchlorate disappears, a is the initial quantity of perchlorate present, *in moles per g.-atom of carbon*, and x is the amount of perchlorate which has reacted (in the same units) at time t.

In Eq. 4 the reaction rate is proportional to the surface area of potassium perchlorate, represented by the factor $(a - x)^{2/3}$. The equation thus takes into account the influence of the size of the perchlorate particles. The rate coefficient k contains a factor which is

dependent on the radius r of the perchlorate particles but, as in the present study the perchlorate particle size has been generally kept constant, r does not appear explicitly in the equation. A more general form of Eq. 4 would be

$$dx/dt = k(a - x)^{2/3}/r^2x^{1/3}$$

By using this expression, practically coincident straight lines were obtained on plotting kt against t from the experimental curves shown in Fig. 1.

The reaction rate is furthermore dependent on the initial ratio of the reactants, as both a and x are expressed in units based on the perchlorate : carbon ratio. The factor $x^{1/3}$ represents the amount of potassium chloride formed, which must obviously appear as a divisor, as the chloride lowers the reaction rate, forming a barrier between the reactants. In the case of slabs of planar reactants pressed together, the thickness of the dividing layer (represented by y in Eq. 1*a*) should be proportional to x and for reactants of various shapes to x^n, where n must be smaller than unity. No theoretical explanation can be given by us for the occurrence of the power of 1/3.

Eq. 4 can be written thus :

$$kt = \int_0^x x^{1/3}dx/(a - x)^{2/3} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(Eq. 5)}$$

This integral can be solved by developing it into a series, the members of which can be integrated in turn :

$$kt = 3(x^2/a)^{2/3}[0{\cdot}25 + (0{\cdot}28571x/3a) + 0{\cdot}5(x/3a)^2 + \ldots] \quad . \quad . \quad \text{(Eq. 6)}$$

For the evaluation of the experimental results it proved to be sufficient to take into consideration only the first three members of the series. Fig. 4 shows the graphical representation of kt–t according to Eq. 6, from the experimental values shown in Fig. 3 for different mixtures of potassium perchlorate and Nuchar. Very nearly coincident lines were also obtained in the same manner for the reactions of other mixtures employed in this investigation (see Table 2). Eq. 6 is valid only as long as the surface area of the carbon is large in comparison with that of the perchlorate. This can be seen for instance from the rate coefficients in Table 2, representing the reaction rate of different amounts of potassium

TABLE 2. *Rate coefficients calculated from kt–t curves* (Eq. 6).

Reactants	Molar ratio oxidant : carbon	t	10^4k (min.$^{-1}$) *
$KClO_4$–Nuchar	0·25 : 1	343°	5·2
,, ,, ...	0·50 : 1	,,	5·0
,, ,, ...	1·0 : 1	,,	5·5
,, ,, ...	2·0 : 1	,,	4·4
$KClO_4$–sugar charcoal	0·25 : 1	367	4·6
,, ,, ...	0·50 : 1	,,	4·85
,, ,, ...	1·0 : 1	,,	4·5
,, ,, ...	2·0 : 1	,,	4·0
$KClO_4$–carbon black	0·25 : 1	367	13
,, ,, ...	0·50 : 1	,,	12·2
,, ,, ...	1·0 : 1	,,	12·1
,, ,, ...	5·0 : 1	,,	4·2
KIO_3–sugar charcoal	0·33 : 1	379	55
,, ,, ...	0·66 : 1	,,	41
,, ,, ...	1·33 : 1	,,	29

* The dimension of the rate coefficient is min.$^{-1}$, as both a and x (being expressed in moles per g.-atom of carbon) are dimensionless. As the rate expression (Eq. 4) is valid only as long as the surface area of the carbon is comparatively very large, the formal analogy of the dimension of this rate coefficient to that of a general first-order rate coefficient is not unexpected.

perchlorate with carbon black.* In general, Eq. 6 appears to hold only for the steep portion of the reaction curves, and in the latter stages of the reaction the experimental falls below the calculated rate. Table 2 shows the values of the rate coefficients as calculated

* These rate coefficients were recalculated from the experimental results of a previous paper (Patai and Hoffmann, *loc. cit.*).

by means of Eq. 6 from *kt–t* graphs, consideration being given to the experimental points only up to about 100 minutes.

This investigation has been carried out under the auspices of the Scientific Department, Israeli Ministry of Defence, and is published with its permission. The authors are indebted to Prof. E. D. Hughes, F.R.S., and to Dr. H. J. G. Hayman for valuable suggestions and help in the writing of this paper.

Laboratories of the Scientific Department, Ministry of Defence, Israel.
Department of Organic Chemistry,
The Hebrew University, Jerusalem. [*Received, January 26th*, 1955.]

Synthesis of αβ-Unsaturated Glycerides.

By G. I. Fray and N. Polgar.

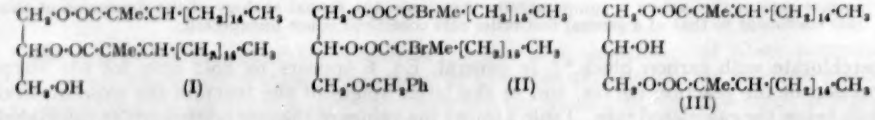
[Reprint Order No. 6096.]

1 : 2-Di-*O*-2′-methyloctadec-2′-enoylglycerol has been synthesised by two different routes. Catalytic hydrogenolysis of 1-*O*-benzyl-2 : 3-di-*O*-2′-methyloctadec-2′-enoylglycerol in the presence of palladium black removes the benzyl group without reducing the αβ-unsaturated acyl groups. An alternative procedure involves reaction of 1-*O*-benzylglycerol with 2-bromo-2-methyloctadecanoyl bromide, followed by catalytic hydrogenolysis and pyridine dehydrobromination of the resulting bromo-substituted diglyceride. 1 : 3-Di-*O*-2′-methyloctadec-2′-enoylglycerol is also prepared.

The present work was undertaken in connection with studies of the lipids of tubercle bacilli. Various lipid fractions from human tubercle bacilli, including the phospholipids, yield on hydrolysis dextrorotatory mixtures of acids of which a main constituent, mycolipenic acid, is now known to be (+)-2 : 4 : 6-trimethyltetracos-2-enoic acid (Bailey, Polgar, and Robinson, *J.*, 1953, 3031; Polgar, *J.*, 1954, 1008). The phospholipid fraction has been shown to consist of glycerinositophosphatides (de Sütö-Nagy and Anderson, *J. Biol. Chem.*, 1947, **171**, 749, 761), and it was, therefore, of interest to study the preparation of αβ-unsaturated glycerides, as possible intermediates towards syntheses of related phosphatides.

The present communication deals with the synthesis of some simple αβ-unsaturated diglycerides, with 2-methyloctadec-2-enoic acid (Bailey, Polgar, Tate, and Wilkinson, *J.*, 1955, 1547) as the acid constituent. The requisite intermediates for the preparation of phospholipids derived from 1-glycerophosphoric acid (α-phosphatidic acids) are 1 : 2-diglycerides. For obtaining the latter, hydrogenolysis is usually employed to remove groups blocking the 3-position of glycerol after the acyl groups have been introduced. Accordingly, only saturated 1 : 2-diglycerides have been prepared by these procedures.

Since αβ-unsaturated acids undergo catalytic hydrogenation less readily than those with non-conjugated double bonds, it appeared that esters of 1-*O*-benzylglycerol with αβ-unsaturated acids, on partial catalytic hydrogenation, might lose the benzyl group without reduction of the acyl residues. This proved so. 1-*O*-Benzylglycerol was converted, by reaction with 2-methyloctadec-2-enoyl chloride, into its diacyl derivative. This on hydrogenation in the presence of palladium black afforded 1 : 2-di-*O*-2′-methyloctadec-2′-enoylglycerol (I).



An alternative route involved bromination of 2-methyloctadecanoic acid in the presence of red phosphorus (Hell–Volhard–Zelinsky) and reaction of the resulting α-bromo-acid

bromide with 1-*O*-benzylglycerol to yield the bromo-substituted diacylbenzylglycerol (II). Catalytic hydrogenolysis of the benzyl group, followed by dehydrobromination of the product by pyridine, gave the αβ-unsaturated diglyceride (I).

1 : 3-Di-*O*-2′-methyloctadec-2′-enoylglycerol (III) was prepared by known procedures (cf. Gupta and Malkin, *J.*, 1952, 2405) *via* the monoacyl derivative of *O*-*iso*propylideneglycerol.

Experimental

Ultraviolet spectra were determined, for MeOH solutions, by Mr. F. Hastings and Dr. F. B. Strauss. M. p.s were determined by means of a hot-stage microscope.

1 : 2-*Di*-O-2′-*methyloctadec*-2′-*enoylglycerol*.—(i) 2-Methyloctadec-2-enoyl chloride (5·2 g.), prepared from 2-methyloctadec-2-enoic acid (Bailey, Polgar, Tate, and Wilkinson, *loc. cit.*) by means of oxalyl chloride, in carbon tetrachloride (10 c.c.) was added to a mixture of 1-*O*-benzylglycerol (1·5 g.) (Howe and Malkin, *J.*, 1951, 2663), pyridine (1·3 g.), and carbon tetrachloride (20 c.c.). The mixture was kept overnight at the room temperature, then at 40° for 12 hr. The product was taken up in ether, and the ethereal solution washed, successively, with 1% hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the solvent gave the diacyl derivative (4·7 g.) which was hydrogenated in *n*-hexane (20 c.c.) and glacial acetic acid (a few drops) in the presence of palladium black (0·6 g.; Willstätter and Waldschmidt-Leitz, *Ber.*, 1921, **54**, 113) at room temperature and pressure. The theoretical amount of hydrogen (1 H_2) was absorbed after 12 hr. Filtration of the solution, and removal of the solvent under reduced pressure gave the 1 : 2-*diglyceride* (3·5 g.), m. p. 42° after crystallisation from ethanol at 0° (Found : C, 75·8; H, 11·6. $C_{41}H_{76}O_5$ requires C, 75·9; H, 11·8%). Ultraviolet absorption : max. at 2180 Å (log ε 4·37).

(ii) 2-Methyloctadecanoic acid (12 g.) was heated with bromine (23 g.) in the presence of red phosphorus (1·2 g.) for 6 hr. (cf. Bailey, Polgar, Tate, and Wilkinson, *loc. cit.*). Distillation of the product gave the bromo-acid bromide as a pale yellow oil (13 g.), b. p. 225—235°/6 mm. This was added to 1-*O*-benzylglycerol (2·7 g.) and pyridine (2·3 g.) in carbon tetrachloride (30 c.c.) and the mixture kept at the room temperature overnight, then at 40° for 12 hr. The product, isolated in the usual manner, was hydrogenated as above until the theoretical amount of hydrogen was taken up (7 days). After removal of the catalyst and solvent the product (a 3·8-g. portion) was refluxed with pyridine (12 g.) for 16 hr., then worked up in the manner previously described for similar dehydrobrominations (Bailey, Polgar, Tate, and Wilkinson, *loc. cit.*). 1 : 2-Di-*O*-2′-methyloctadec-2′-enoylglycerol (1 g.) was obtained as a pale yellow solid (Found : C, 75·8; H, 11·5%), absorption max. at 2180 Å (log ε 4·35).

The diglyceride gave on hydrolysis with ethanolic potassium hydroxide 2-methyloctadec-2-enoic acid (Found : C, 76·7; H, 12·2. Calc. for $C_{19}H_{36}O_2$: C, 77·0; H, 12·2%), absorption max. at 2140 Å (log ε 4·12).

1 : 3-*Di*-O-2′-*methyloctadec*-2′-*enoylglycerol*.—Gupta and Malkin's procedure (*loc. cit.*) was employed. Reaction between 2-methyloctadec-2-enoyl chloride (5 g.) and *iso*propylideneglycerol (2·1 g.) in benzene (30 c.c.) in the presence of pyridine (1·3 g.) gave the acyl derivative as a pale yellow oil (3·4 g.). To a solution of this in ether (10 c.c.), cooled in ice, was added ice-cold concentrated hydrochloric acid (10 c.c.) with vigorous shaking, and the mixture kept at 0° for 0·5 hr. Ice-water (50 c.c.) was then gradually added and the product (2·8 g.) isolated by means of ether. It was then subjected to the action of 2-methyloctadec-2-enoyl chloride (2·4 g.) in benzene (50 c.c.) in the presence of pyridine (0·6 g.). The resulting crude diglyceride (4·7 g.) was chromatographed in benzene on a silica column prepared in the same solvent. Elution with ether–benzene (1 : 25) gave the *diglyceride*, m. p. 47—49° after crystallisation from ethanol at 0° (Found : C, 76·0; H, 11·7. $C_{41}H_{76}O_5$ requires C, 75·9; H, 11·8%), absorption max. at 2160 Å (log ε 4·44).

Dyson Perrins Laboratory, Oxford University. [*Received, February 2nd*, 1955.]

Quinoxalines and Related Compounds. Part I. The Methylation of Some 2- and 3-Hydroxyquinoxalines.

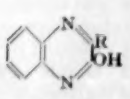
By G. W. H. Cheeseman.

[Reprint Order No. 6128.]

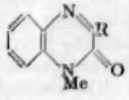
The methylation of 2-hydroxyquinoxaline and five other 2- and 3-hydroxyquinoxalines is described and discussed. Methyl sulphate gives *N*-methyl derivatives: 2-amino-3-hydroxyquinoxaline (I; R=NH_2) is converted by methyl sulphate into 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2) and not, as previously reported, into the isomeric *O*-methyl derivative (III; R = NH_2). With diazomethane 2-hydroxyquinoxaline (I; R = H) forms 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) and 2-methoxyquinoxaline (III; R = H), but the other hydroxyquinoxalines studied yield mixtures of *N*- and *O*-methyl derivatives.

The methylation of 2- and 3-hydroxyquinoxalines with a variety of reagents leads to both *N*- and *O*-methyl derivatives (Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publ. Ltd., London, 1953, p. 241), but the correlation between reagent and product is unpredictable. In this paper the methylation of 2-hydroxyquinoxaline (I; R = H) and five other 2- and 3-hydroxyquinoxalines is described and discussed. In each case, methyl sulphate and alkali gave the *N*-methyl derivative. Mixtures of *N*- and *O*-methyl derivatives were obtained with diazomethane, except in the case of 2-hydroxyquinoxaline where *N*-, *O*-, and *C*-methylation took place.

When 7-hydroxypteridine was treated with excess of diazomethane, a dimethyl derivative was formed (Albert, Brown, and Cheeseman, *J.*, 1952, 1620). This compound has been shown to be 7 : 8-dihydro-6 : 8-dimethyl-7-oxopteridine (Albert, Brown, and Wood, personal communication). The parallel reaction between 2-hydroxyquinoxaline (I; R = H) and diazomethane has now been investigated; it gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) and 2-methoxyquinoxaline (III; R = H). When 2-hydroxyquinoxaline was treated with methyl sulphate and alkali 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) was formed. This compound yielded the above *CN*-dimethyl derivative (II; R = Me) on methylation with diazomethane and may therefore be an intermediate in the conversion of 2-hydroxyquinoxaline into 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline. The *N*-methylation of 2-hydroxyquinoxaline with methyl sulphate is a more convenient route to 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) than the previous method involving a multi-stage synthesis from *N*-methyl-*o*-phenylenediamine (King and Clark-Lewis, *J.*, 1951, 3379; Kuhling and Kaselitz, *Ber.*, 1906, **39**, 1314).



(I)



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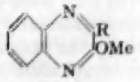

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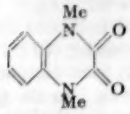

(IV)

2-Methoxyquinoxaline was readily prepared by the action of sodium methoxide on 2-chloroquinoxaline and conveniently isolated as a picrate; it did not react with diazomethane.

Ohle, Gross, and Wolter (*Ber.*, 1937, **70**, 2148) obtained 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) when 2-hydroxy-3-methylquinoxaline (I; R = Me) was treated with diazomethane. This derivative was, however, prepared in higher yield when methyl sulphate was used (Cook and Perry, *J.*, 1943, 394). A further examination of the diazomethane reaction has now shown that both the *N*-methyl derivative (II; R = Me) and the *O*-methyl derivative (III; R = Me) were formed. The latter was prepared in high yield from sodium methoxide and 2-chloro-3-methylquinoxaline.

A number of 2 : 3-dihydroxyquinoxalines have been treated with methyl sulphate and alkali and the dimethyl derivatives obtained formulated as 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxalines (Newbold and Spring, *J.*, 1948, 519; Crowther, Curd, and Stacey, *J.*, 1949, 1260; Curd, Davey, and Stacey, *J.*, 1949, 1271; see, however, Landquist, *J.*, 1953, 2816). Newbold and Spring showed that the product from 2 : 3-dihydroxyquinoxaline (I; R = OH) was not 2 : 3-dimethoxyquinoxaline (III; R = OMe) but Simpson (*op. cit.*) has pointed out that the possibility of *ON*-methylation was not excluded. *ON*-Methylation occurred when 1 : 4-dihydroxyphthalazine was treated with methyl sulphate and alkali (Rowe and Peters, *J.*, 1933, 1331). Proof that 2 : 3-dihydroxyquinoxaline was converted into 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) by methyl sulphate has now been obtained by the synthesis of this compound from *NN'*-dimethyl-*o*-phenylenediamine and ethyl oxalate. When 2 : 3-dihydroxyquinoxaline was treated with diazomethane, *NN*-, *ON*-, and *OO*-methylation took place and thus (IV), 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe), and 2 : 3-dimethoxyquinoxaline were formed. The *ON*-dimethyl compound (II; R = OMe) was readily synthesised by the action of sodium methoxide on 3-chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = Cl), which was itself prepared from the corresponding hydroxyquinoxaline (II; R = OH) by chlorination with phosphoryl chloride. If phosphorus pentachloride is used as the chlorinating agent the hydroxy-compound is converted into 2 : 3-dichloroquinoxaline (Usherwood and Whiteley, *J.*, 1923, 1084).

1 : 2 : 3 : 4-Tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) was obtained from 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) by use of methyl sulphate. Diazomethane gave also the isomeric *O*-methyl derivative (II; R = OMe). 2-Hydroxy-3-methoxyquinoxaline (I; R = OMe), prepared by the alkaline hydrolysis of 2-chloro-3-methoxyquinoxaline, was converted into 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) by methyl sulphate. Reaction with diazomethane yielded (II; R = OMe) and 2 : 3-dimethoxyquinoxaline (III; R = OMe) and thus both *N*- and *O*-methylation took place.

As methyl sulphate had proved to be an *N*-methylating agent for the above mentioned hydroxyquinoxalines, it was decided to re-investigate the report (Stevens, Pfister, and Wolf, *J. Amer. Chem. Soc.*, 1946, **68**, 1035) that *O*-methylation occurred when 2-amino-3-hydroxyquinoxaline (I; R = NH_2) was treated with dimethyl sulphate and alkali. The product had m. p. 264—270°, and was assumed to be 2-amino-3-methoxyquinoxaline (III; R = NH_2), as a compound, m. p. above 260°, and of the same carbon and hydrogen content, had been isolated in small yield from the reaction of 2-chloro-3-methoxyquinoxaline (III; R = Cl) and methanolic ammonia (*idem*, *loc. cit.*). It should also be possible to prepare the methoxy-amine (III; R = NH_2) by treating 2-amino-3-chloroquinoxaline with sodium methoxide, and when this reaction was carried out, a product, m. p. 151—152°, was obtained in excellent yield. This compound readily gave 2-amino-3-hydroxyquinoxaline on hydrolysis with 2·5N-hydrochloric acid at 100° and must therefore be the true 2-amino-3-methoxyquinoxaline (III; R = NH_2). The compound obtained from the methyl sulphate methylation of 2-amino-3-hydroxyquinoxaline was, however, resistant to the action of 2·5N-hydrochloric acid at 100°. It was shown to be the *N*-methyl derivative of the hydroxyquinoxaline, 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2), by the synthesis of this compound in high yield by amination of 1 : 2-dihydro-1-methyl-2-oxo-3-phenoxyquinoxaline (II; R = OPh). The reaction of diazomethane and 2-amino-3-hydroxyquinoxaline yielded the expected mixture of *N*- and *O*-methyl derivatives (II and III; R = NH_2).

The preparation of 2-methoxy-3-phenoxyquinoxaline (III; R = OPh) and improved methods for obtaining several known quinoxalines are also described below.

Experimental

Aluminium oxide (Spence, type H, mesh 100—200) was used.

1 : 2-Dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) was prepared by the method of Cook and Perry (*loc. cit.*), 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) by that of

King and Clark-Lewis (*loc. cit.*), and 2 : 3-dimethoxyquinoxaline (III; R = OMe) by that of Newbold and Spring (*loc. cit.*).

2-Methoxyquinoxaline Picrate.—2-Chloroquinoxaline (2·3 g.; Gowenlock, Newbold, and Spring, *J.*, 1945, 622) in methanol (10 c.c.) was added to a solution of sodium methoxide, prepared from sodium (0·41 g.) and methanol (10 c.c.). The mixture was heated under reflux for 2 hr. and then poured into water. Extraction with ether, and evaporation of the dried (Na_2SO_4) extracts, gave 2-methoxyquinoxaline (III; R = H) (2·2 g., 98%) as an oil which crystallised as long colourless needles, m. p. *ca.* 31—33°. The *picrate*, prepared in methanol, had m. p. 141—142° (Found: C, 46·1; H, 2·75; N, 18·1. $C_{15}H_{11}O_8N_5$ requires C, 46·3; H, 2·85; N, 18·0%).

Methylation of 2-Hydroxyquinoxaline (I; R = H).—(a) *With diazomethane.* Ethereal diazomethane (from methylnitrosourea, 10·3 g.) was added to an ice-cooled suspension of 2-hydroxyquinoxaline (1·46 g., 0·01 mole; *idem, loc. cit.*) in dry methanol (20 c.c.). The mixture was left overnight at 0° and solvent and excess of diazomethane were then removed in a vacuum. The residue was dissolved in benzene (10 c.c.), and the solution filtered through a column of aluminium oxide prepared in benzene. Elution with benzene and benzene–ether (3 : 1) gave 2-methoxyquinoxaline (III; R = H) (0·42 g., 26%) as colourless needles, m. p. *ca.* 30°. The picrate had m. p. 141—142° (undepressed when mixed with an authentic specimen). Mixed crystalline solid (0·20 g.) was also removed from the column with benzene–ether (3 : 1). Elution with benzene–ether (1 : 1) and ether gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (0·87 g., 50%), m. p. and mixed m. p. 85—86°. The *picrate* crystallised from methanol as yellow plates, m. p. 144—145° (Found: C, 47·7; H, 3·2; N, 17·8. $C_{16}H_{13}O_8N_5$ requires C, 47·65; H, 3·25; N, 17·4%).

(b) *With methyl sulphate.* Methyl sulphate (6 c.c.) was added to 2-hydroxyquinoxaline (1·46 g.) in 2N-sodium hydroxide (60 c.c.). The mixture was shaken until clear (about 10 min.) and then left overnight at room temperature. Extraction with chloroform, and evaporation of the dried (Na_2SO_4) extracts, gave a residue (1·1 g.), m. p. (mainly) 114—120°, which on crystallisation from light petroleum (b. p. 80—100°; 30 parts) yielded 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H), m. p. and mixed m. p. 120—121°.

Methylation of 1 : 2-Dihydro-1-methyl-2-oxoquinoxaline (II; R = H).—Ethereal diazomethane (from methylnitrosourea, 5·2 g.) was added to an ice-cooled suspension of the quinoxaline (1·6 g.) in dry methanol (20 c.c.). The mixture was left at 0° overnight, and solvent and excess of diazomethane were then removed in a vacuum leaving a residue, m. p. 72—81°. Crystallisation from acetone–water (2 : 1; 4 parts) gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (1·2 g., 70%), m.p. and mixed m. p. 83—85°.

2-Methoxy-3-methylquinoxaline (III; R = Me).—2-Chloro-3-methylquinoxaline (1 g.; *idem, loc. cit.*) in methanol (10 c.c.) was added to a solution of sodium methoxide (1·25 equivs.), prepared from sodium (0·17 g.) and methanol (10 c.c.). The mixture was heated under reflux for 2 hr. and solvent then removed in a vacuum. Water was added to the residue, and the crystalline precipitate of *2-methoxy-3-methylquinoxaline* (0·9 g., 92%), m. p. 67—69°, collected. Crystallisation from methanol–water (2 : 1) gave colourless needles, m. p. 68—69° (Found: C, 68·9; H, 6·0; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 68·95; H, 5·8; N, 16·05%).

Methylation of 2-Hydroxy-3-methylquinoxaline (I; R = Me).—The hydroxyquinoxaline (1·6 g., 0·01 mole; Hinsberg, *Annalen*, 1896, 292, 245) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, and the product dissolved in benzene and fractionated on a column of aluminium oxide. Elution with benzene yielded 2-methoxy-3-methylquinoxaline (III; R = Me) (0·53 g. 30%), m. p. and mixed m. p. 69—70°, and a crystalline solid (0·14 g.), m. p. (mainly) 81—84°. 1 : 2-Dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (0·88 g., 51%), m. p. and mixed m. p. 85—86°, was removed from the column with benzene–ether (3 : 1 and 1 : 1).

N-Methyl-o-phenylenediamine.—The diamine was prepared by the method of Usherwood and Whiteley (*loc. cit.*) and Phillips (*J.*, 1929, 2820) except that it was found more convenient to reduce *N*-methyl-*o*-nitroaniline catalytically. The nitro-amine was hydrogenerated in ethanol over 5% palladium–charcoal at room temperature and pressure. Removal of catalyst and solvent gave the diamine as a dark oil: it was used as such.

1 : 2-Dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH).—This was prepared by Usherwood and Whiteley's method (*loc. cit.*), modified as follows. *N*-Methyl-*o*-phenylenediamine (from the reduction of 11·3 g. of *N*-methyl-*o*-nitroaniline) and ethyl oxalate (20 g.) were heated at 160—165° (bath temp.) for 2 hr. After cooling, the separated solid (12 g., 92%), m. p. 284—285°, was filtered off and washed with ethanol. Crystallisation from water (70 parts)

(charcoal) gave colourless needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline, m. p. 286—287°.

3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = Cl).—The above hydroxy-compound (7·5 g.) and freshly distilled phosphoryl chloride (40 c.c.) were heated under reflux for 1½ hr. The resulting dark green solution was slowly poured into stirred ice-water, and the precipitated solid filtered off, washed with water, dried, and extracted with light petroleum (Soxhlet). The petroleum extract yielded pale yellow needles of *3-chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline* in two crops (total 5·5 g.), m. p. 131—133°. The original filtrate was extracted with ether, and the combined extracts were washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Evaporation of solvent gave a further 1·1 g., m.p. 131—133° (total yield 80%). The m. p. was unchanged by further crystallisation from light petroleum (b. p. 60—80°) (Found: C, 55·7; H, 3·35; N, 14·5; Cl, 18·05. $C_9H_7ON_2Cl$ requires C, 55·55; H, 3·6; N, 14·4; Cl, 18·2%). 3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline was rapidly hydrolysed to the hydroxy-compound (II; R = OH) in hot aqueous methanol.

1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe).—This compound was prepared similarly to 2-methoxy-3-methylquinoxaline. 3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·62 g.) was converted into a product (0·5 g.), m. p. (mainly) 122—123°. Crystallisation from benzene–light petroleum (1 : 1) gave colourless needles of *1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline*, m. p. 122—123° (Found: C, 63·3; H, 5·4; N, 14·7. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·7%).

A solution of the methoxy-compound (0·38 g.) in ethanol (8 c.c.) and hydrochloric acid (*d* 1·18; 2 c.c.) was heated under reflux for 1 hr. On cooling to 0°, the mixture deposited needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) (0·31 g., 88%), m. p. and mixed m. p. 285—286°.

1 : 2 : 3 : 4-Tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV).—A mixture of *NN'*-dimethyl-*o*-phenylenediamine (1·36 g.; Elderfield and Meyer, *J. Amer. Chem. Soc.*, 1954, **76**, 1887) and ethyl oxalate (4 g.) was heated under reflux for 1 hr. After cooling, the crystalline precipitate (0·7 g; m.p. 250—253°) was filtered off and washed with ethanol. A further crop (0·3 g.; m. p. 246—248°) was obtained by vacuum-concentration of the mother-liquor. Crystallisation from ethanol (50 parts) (charcoal) gave colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (0·7 g., 37%), m. p. 252—253°. The m. p. was not raised by further crystallisation.

Methylation of 2 : 3-Dihydroxyquinoxaline (I; R = OH).—(a) *With diazomethane.* The dihydroxyquinoxaline (1·62 g., 0·01 mole; Newbold and Spring, *loc. cit.*) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 2 hr. The product was heated under reflux with benzene (15 c.c.) and, after cooling, the crystalline precipitate of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (0·24 g.; m. p. and mixed m. p. 252—253°) was filtered off. The filtrate was then passed through a column of aluminium oxide prepared in benzene. Elution with benzene gave 2 : 3-dimethoxyquinoxaline (III; R = OMe) (0·42 g., 22%), m. p. and mixed m. p. 92—93°. 1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (0·99 g., 52%), m. p. and mixed m. p. (mainly) 121—123°, was removed from the column with ether and ether–methanol (9 : 1). Elution with ether–methanol (9 : 1) also yielded a further quantity of the dimethyl derivative (IV) (0·15 g.), m. p. (mainly) 245—251° (total yield 21%).

(b) *With methyl sulphate.* The dihydroxy-compound was treated with methyl sulphate and alkali as described by Newbold and Spring (*loc. cit.*). Colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) were obtained, m. p. 252—253° (undepressed when mixed with a specimen prepared as described above). Newbold and Spring give m. p. 256—258°.

Methylation of 1 : 2-Dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH).—(a) *With diazomethane.* The hydroxyquinoxaline (1·76 g., 0·01 mole) was caused to react with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 3 hr. The product was heated under reflux with benzene (25 c.c.) and, after cooling, the crystalline precipitate of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (0·82 g., 43%), m. p. and mixed m. p. 248—252°, was filtered off. The filtrate was then passed through a column of aluminium oxide prepared in benzene. Elution with benzene–ether (3 : 1) gave 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1 g., 53%), m. p. and mixed m. p. 122—123°.

(b) *With methyl sulphate.* Methyl sulphate (1·26 c.c.) was shaken with a solution of the hydroxyquinoxaline (1·76 g.) in 5% aqueous potassium hydroxide (20 c.c.) (about 5 min.).

Colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (1·4 g.; m. p. 250—252°) were soon deposited; these were collected after cooling to 0°. The mother-liquor was extracted with chloroform and evaporation of the dried (Na_2SO_4) extracts gave a further 0·35 g., m. p. (mainly) 246—248° (total yield 92%).

2 : 3-*Dichloroquinoxaline*.—2 : 3-Dihydroxyquinoxaline (I; R = OH) (15 g.) was heated under reflux with freshly distilled phosphoryl chloride (45 c.c.) and diethylaniline (15 g.) for 2½ hr. The cooled mixture was slowly poured into stirred ice-water, and the precipitated 2 : 3-dichloroquinoxaline (18 g., 98%), m. p. (mainly) 152—155°, filtered off and washed with water. Crystallisation from benzene gave pale yellow needles, m. p. 151—153°.

2-*Chloro*-3-*methoxyquinoxaline*.—This was prepared by the method of Stevens *et al.* (*loc. cit.*), modified as follows. A solution of sodium methoxide, prepared from sodium (1·73 g.) and methanol (100 c.c.), was added dropwise in 3 hr. to a stirred suspension of 2 : 3-dichloroquinoxaline (15 g.) in boiling methanol (250 c.c.). The undissolved solid gradually went into solution. The mixture was heated under reflux for a further 3 hr., and then concentrated to 100 c.c. After cooling to 0°, the precipitate of mixed crystalline solid was collected and ground with water (to remove salt). 2-Chloro-3-methoxyquinoxaline (11·6 g., 79%), m. p. 74—77°, was obtained by filtration. Crystallisation from methanol gave needles, m. p. 79—80° (Found: C, 56·05; H, 3·9; N, 14·3; Cl, 17·9%). Stevens *et al.* give m. p. 74—75°.

2-*Hydroxy*-3-*methoxyquinoxaline* (I; R = OMe).—2-Chloro-3-methoxyquinoxaline (5 g.) was heated with potassium hydroxide (10 g.) in water (50 c.c.) and methanol (100 c.c.) under reflux for 17 hr. After cooling and dilution with water (200 c.c.), the pale yellow solution was thoroughly extracted with ether to remove any unchanged starting material. The aqueous layer was warmed to remove dissolved ether and then acidified with acetic acid. The precipitated *hydroxy-compound* (3·9 g., 86%), m. p. 238—241° (decomp.), crystallised from methanol as pale yellow needles, m. p. 243—244° (decomp.) (Found: C, 61·5; H, 4·65; N, 16·1. $C_9H_8O_2N_2$ requires C, 61·35; H, 4·6; N, 15·9%).

Methylation of 2-*Hydroxy*-3-*methoxyquinoxaline* (I; R = OMe).—(a) *With diazomethane*. The hydroxyquinoxaline (1·76 g., 0·01 mole) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 3 hr. The product was dissolved in benzene and fractionated on a column of aluminium oxide. Elution with benzene gave 2 : 3-dimethoxyquinoxaline (III; R = OMe) (0·77 g., 41%), m. p. and mixed m. p. 92—93°. 1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1·06 g., 56%), m. p. and mixed m. p. 122—123°, was eluted from the column with benzene–ether (1 : 1) and ether.

(b) *With methyl sulphate*. Methyl sulphate (1·26 c.c.) was shaken with a solution of the hydroxyquinoxaline (1·76 g.) in 5% aqueous potassium hydroxide (20 c.c.) (about 15 min.). Colourless crystals of 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1·67 g., 88%; m. p. 118—122°) were soon deposited; these were collected after cooling to 0°.

1 : 2-*Dihydro*-1-*methyl*-2-*oxo*-3-*phenoxyquinoxaline* (II; R = OPh).—3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = Cl) (1·95 g.) was heated with phenol (10 g.) containing potassium hydroxide (0·67 g.) at 95° for 3 hr. The mixture was poured into excess of 2N-sodium hydroxide, and the precipitated solid filtered off and washed with water. Crystallisation from methanol (25 parts) gave 1 : 2-*dihydro*-1-*methyl*-2-*oxo*-3-*phenoxyquinoxaline* (2·0 g., 79%) as colourless needles or plates, m. p. 170—172° (Found: C, 71·2; H, 5·0; N, 11·2. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%).

A solution of the phenoxy-compound (0·4 g.) in ethanol (8 c.c.) and hydrochloric acid (*d* 1·18; 2 c.c.) was heated under reflux for 1 hr. On cooling to 0°, the mixture deposited needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) (0·25 g., 89%), m. p. and mixed m. p. 285—286°.

3-*Amino*-1 : 2-*dihydro*-1-*methyl*-2-*oxoquinoxaline* (II; R = NH_2).—(*a*) The above phenoxy-compound (1·5 g.) was heated with ammonium acetate (9 g.) which had been previously heated to 180° and allowed to cool to 160°. The temperature was raised during 5 min. to 200° and maintained at 200—215° for 15 min. (cf. Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104). When cold, the melt was diluted with water and the crystalline precipitate of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·87 g., 84%), m. p. 273—275°, filtered off (Found: C, 62·0; H, 5·1; N, 24·0. Calc. for $C_9H_9ON_3$: C, 61·7; H, 5·2; N, 24·0%).

(*b*) A solution of 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (0·95 g.) in methanol (20 c.c.; saturated at room temperature with ammonia) was heated in a sealed tube at 140—145° for 8 hr. The separated solid (0·25 g.) was collected by filtration;

it gave colourless needles of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline, m. p. and mixed m. p. 273—274°, after successive crystallisation (charcoal) from methanol (500 parts) and water (1500 parts). Evaporation of the original methanolic mother-liquor gave a residue (0·7 g.) consisting mainly of unchanged starting material.

3-Amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·5 g.) and 2·5N-hydrochloric acid (20 c.c.) were heated on the water-bath for 1 hr. The mixture was made strongly alkaline with 10% aqueous sodium hydroxide, and the precipitated unchanged amino-compound (0·45 g.) was collected.

2-Amino-3-methoxyquinoxaline (III; R = NH_2).—This compound was prepared similarly to 2-methoxy-3-methylquinoxaline above, except that the mixture was heated under reflux for 1 hr. 2-Amino-3-chloroquinoxaline (7·2 g.; Haworth and Robinson, *J.*, 1948, 777) was converted into a product (6·95 g.), m. p. 148—152°. Crystallisation from benzene (5 parts) gave yellow prisms of *2-amino-3-methoxyquinoxaline*, m. p. 151—152° (Found: C, 62·1; H, 5·25; N, 24·0; OMe, 18·25. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0; OMe, 17·7%).

A mixture of 2-amino-3-methoxyquinoxaline (1·75 g.) and 2·5N-hydrochloric acid (25 c.c.) was heated on the water-bath for 1 hr., then basified with 6N-ammonia, and the precipitated 2-amino-3-hydroxyquinoxaline (I; R = NH_2) (1·6 g.; m. p. above 360°) was filtered off and washed with water. A portion was converted into 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2), m. p. and mixed m. p. 273—274°, as described below.

Methylation of 2-Amino-3-hydroxyquinoxaline (I; R = NH_2).—(a) *With diazomethane.* The hydroxyquinoxaline (1·61 g., 0·01 mole; Stevens *et al.*, *loc. cit.*) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 4 hr. and then left at 0° for 3 days. The product was extracted with cold 5% aqueous sodium hydroxide (30 c.c.), and the solid (0·97 g.), obtained by filtration, washed with 5% aqueous sodium hydroxide and water, dried, and then heated under reflux with light petroleum (b. p. 60—80°; 150 c.c.). 3-Amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2) (0·65 g., 37%), m. p. 268—271°, was filtered off; the filtrate was concentrated to *ca.* 10 c.c. and on cooling deposited yellow prisms of 2-amino-3-methoxyquinoxaline (III; R = NH_2) (0·22 g., 13%), m. p. 149—152°. The initial alkaline filtrate gave unchanged 2-amino-3-hydroxyquinoxaline (0·48 g.) on acidification with acetic acid.

(b) *With methyl sulphate.* The hydroxyquinoxaline was treated with methyl sulphate and alkali as described by Stevens *et al.* (*loc. cit.*) and the m. p. of the crude product raised to 274—275° by successive crystallisation from methanol and water (charcoal). The m. p. was not depressed on admixture with an authentic specimen of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline. Stevens *et al.* give m. p. 264—270°.

2-Methoxy-3-phenoxyquinoxaline (III; R = OPh).—2-Chloro-3-methoxyquinoxaline (1·75 g.) was added to a solution of sodium phenoxide, prepared from phenol (15 g.) and sodium (0·46 g.). The mixture was heated at 95° for 17 hr. and then poured into excess of 2N-sodium hydroxide. The precipitated solid was filtered off and washed with water. Crystallisation from methanol (45 parts) gave *2-methoxy-3-phenoxyquinoxaline* (1·7 g., 75%) as very pale yellow needles, m. p. 134—135·5° (Found: C, 71·4; H, 4·5; N, 11·3%).

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QUEEN ELIZABETH COLLEGE (UNIVERSITY OF LONDON), W.8. [*Received, February 14th*, 1955.]

*The Degradation of Carbohydrates by Alkali. Part XI.** 4-O-*Methyl Derivatives of Glucose and Fructose.*

By J. KENNER and G. N. RICHARDS.

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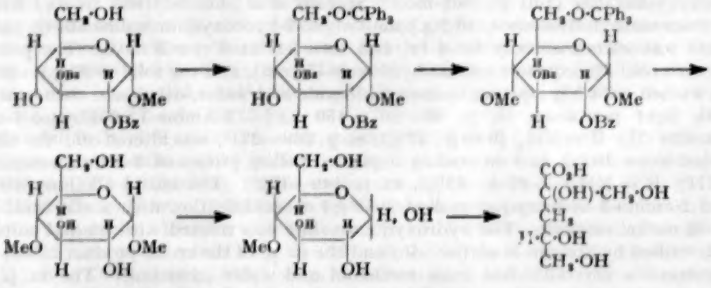
The prediction that D-gluco*iso*saccharinic acids should result from the alkaline degradation of 4-*O*-methyl-D-glucose or -fructose is confirmed.

EVIDENCE has been adduced (*J.*, 1954, 278) that alkaline decomposition of 3-*O*-derivatives of glucose will always furnish the stereoisomeric D-gluco*meta*saccharinic acids and it was suggested that the two D-gluco*iso*saccharinic acids should similarly be produced from the corresponding 4-*O*-derivatives.

This has now been substantiated by the behaviour of 4-*O*-methyl-D-glucose, prepared from methyl 2 : 3-di-*O*-benzyl-α-D-glucoside (Bell and Lorber, *J.*, 1940, 453) by a series of reactions corresponding to that employed by McGilvray (*J.*, 1952, 3648) for the preparation of the 4-*O*-methyl-β-D-glucoside. The simultaneous removal of triphenylmethyl and benzyl



groups, as represented in the scheme, is noteworthy and was conveniently effected by use of Raney nickel. As expected, the same D-gluco*iso*saccharinic acids were also obtained, and more rapidly, by treatment of 4-*O*-methyl-D-fructose with lime-water. Further, the experimental data tabulated below show that acid is not formed from 4-*O*-methyl-D-glucose until conversion into 4-*O*-methyl-D-fructose has set in (cf. *J.*, 1953, 2245).

The generalisation thus confirmed may be applied to the structural investigation of carbohydrate materials. Thus, alkaline degradation of maltose and lactose to D-gluco*iso*saccharinic acids (Dubrunfaut, *Moniteur Scient.*, 1882, 521; Cuisinier, *ibid.*, p. 522), and respectively glucose and galactose (Lobry de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1896, **15**, 96; 1899, **18**, 147) would have revealed that the disaccharides were the 4-*O*-glucosyl- and the 4-*O*-galactosyl-D-hexose respectively had the reaction been then understood. Similarly, the formation of D-gluco*iso*saccharinic acids by the action of lime-water on hydro- and oxy-celluloses (Faber and Tollens, *Ber.*, 1899, **32**, 2596; Murumow, Sack, and Tollens, *ibid.*, 1901, **34**, 1427; Tollens, *ibid.*, p. 1434) would have indicated the chain structure and, almost certainly, also the pyranosidic ring structure which was not assigned to cellulose until later.

Formation of the ordinary, the *meta*-, and the *iso*-type of D-glucosaccharinic acids is in fact diagnostic of 1-, 3-, and 4-*O*-substituted glucose derivatives respectively. Doubtless the same will apply to the acids derived from other monoses, and saccharinic acids are thus to be regarded as reference compounds in carbohydrate chemistry. Although some duplication will occur, *e.g.*, the same *meta*-acids will be derived from glucose, allose, mannose, and altrose, each monose should in general provide a distinct set of acids individually accessible by use of the above generalisation.

* Part X, *J.*, 1955, 1709.

Experimental

The following solvents and sprays were used in paper chromatography: solvent a, butanol–pyridine–water (6 : 4 : 3); spray a, silver nitrate–sodium hydroxide (Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444); spray b, naphtharesorcinol (Hough, Jones, and Wadman, *J.*, 1950, 1702).

Methyl 2 : 3-*Di*-O-*benzyl*-6-O-*triphenylmethyl*-α-D-*glucoside* was prepared by treating a solution of methyl 2 : 3-di-*O*-benzyl-α-D-glucoside (22·0 g.) in dry pyridine (400 ml.) with triphenylmethyl chloride (16·0 g.) at 100° for 2½ hr. The resulting solution, cooled to 0°, was diluted with water (100 ml.) and, after several hours at room temperature, then poured into water. By extraction with water and isolation in the usual way, the 6-O-*triphenylmethyl ether* was obtained as an amorphous solid, $[\alpha]_D^{26}$ +14·5° (*c* 3 in $CHCl_3$) (Found: C, 77·4; H, 6·7; OMe, 5·1. $C_{40}H_{40}O_6$ requires C, 77·9; H, 6·5; OMe, 5·0%). Four successive treatments with silver oxide and methyl iodide in the usual manner converted it into its 4-O-*methyl ether*, a yellow glass, $[\alpha]_D^{20}$ +13° (*c* 2 in $CHCl_3$) (Found: C, 77·8; H, 7·0; OMe, 10·2. $C_{41}H_{42}O_6$ requires C, 78·1; H, 6·7; OMe, 9·8%).

Methyl 4-O-*methyl*-α-D-*glucoside* resulted when the foregoing ether (23·20 g.) in ethanol (200 ml.) was stirred with a suspension of Raney nickel (80 g.) in ethanol (100 ml.) at 60°, rising during 6 hr. to 85°. The solution, after 2 hours' further refluxing, was filtered and evaporated nearly to dryness. Filtration of a solution of the residue in a mixture of water (100 ml.) and chloroform (100 ml.), and evaporation of the aqueous solution after further washing with chloroform (2 × 50 ml.), afforded a colourless syrup (6·17 g.) which, after distillation at 163—165° (bath-temp.)/0·03 mm., had n_D^{18} 1·4810, $[\alpha]_D^{20}$ +15° (*c* 3 in H_2O) (Found: OMe, 30·6. $C_8H_{16}O_6$ requires OMe, 29·8%).

4-*O*-Methyl-D-glucose was produced by heating a solution of the glucoside (2·00 g.) in N-sulphuric acid (25 ml.) 20 hr. at 100°, but the amorphous product (1·43 g.) was found on chromatographic analysis to contain, besides the 4-*O*-methyl-D-glucose (R_F 0·49, solvent a, spray a), traces of glucose (R_F 0·29), and 4 : 6-di-*O*-methyl-D-glucose (R_F 0·62). Elution of the crude product from a cellulose column with *n*-butanol half-saturated with water removed first a very small amount of, probably, a tri-*O*-methyl derivative (R_F 0·72), and then 4 : 6-di-*O*-methyl-D-glucose (m. p. and mixed m. p. 162—163°); further elution with the same solvent and then with 90% methanol yielded pure 4-*O*-methyl-D-glucose as a colourless syrup, $[\alpha]_D^{20}$ +60·8° (*c* 5 in H_2O) (Found: OMe, 15·6. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Pacsu (*Ber.*, 1925, **58**, 1455; cf. Schinle, *Ber.*, 1932, **65**, 315) reported $[\alpha]_D$ +61°. The p-*toluidide*, recrystallised from ethanol–water, had m. p. 159—160° (Found: N, 5·3. $C_{14}H_{21}O_5N$ requires N, 4·95%). The phenylosazone had m. p. 156—157° (Found: N, 14·9. Calc. for $C_{19}H_{24}O_4N_4$: N, 15·05%).

Action of Lime-water on 4-O-*Methyl*-D-*glucose*.—(a) *Qualitative*. A solution of 4-*O*-methyl-D-glucose (1·90 g.) in oxygen-free 0·04N-lime-water (600 ml.) was kept at 35° for 4 days and then at 100° for 1 hr., then saturated with carbon dioxide, boiled for a few minutes, and filtered. Evaporation of the filtrate to dryness yielded a white powder (1·84 g.) which was dissolved in hot water (5 ml.) and fractionally precipitated with ethanol (cf. Corbett and Kenner, *J.*, 1954, 1789), to yield first of all calcium α-D-gluco*iso*saccharinate (0·53 g., from 75% alcohol), $[\alpha]_D^{20}$ −2° (*c* 1 in H_2O), and, after separation of intermediate fractions, calcium β-D-gluco*iso*saccharinate (0·29 g., from 100% alcohol), $[\alpha]_D^{20}$ +3° (*c* 1 in H_2O).

The α-form was readily converted into the crystalline α-D-gluco*iso*saccharinolactone (cf. Corbett and Kenner, *loc. cit.*), m. p. and mixed m. p. 94—96°, while the β-form, treated in the usual manner, yielded the corresponding brucine salt, m. p. 190—195° (decomp.), and, after recrystallisation from ethanol, $[\alpha]_D^{20}$ −20° (*c* 1 in H_2O). Nef (*Annalen*, 1910, **376**, 1) reported m. p. 200—210° (decomp.), $[\alpha]_D^{20}$ −20°.

(b) *Quantitative*. A solution of 4-*O*-methyl-D-glucose (0·275 g.) in oxygen-free 0·0398N-lime-water (100 ml.) was kept at 25°; at intervals samples (5 ml.) were withdrawn, added to 0·05N-sulphuric acid (5 ml.), and then titrated with 0·025N-potassium hydroxide (phenolphthalein). The neutralised solutions were subsequently diluted to 25 ml. and the optical rotations observed in a 4-dm. tube (see Table).

4-O-*Methyl*-D-*fructose*.—The sample of methyl derivative used, kindly supplied by Dr. J. Oldham, had $[\alpha]_D^{21}$ −91·5° (*c* 1 in H_2O) and readily yielded 4-*O*-methylglucose phenylosazone, m. p. and mixed m. p. 156—157°. Hirst, Mitchell, Percival, and Percival give $[\alpha]_D^{18}$ (equil.) −97° (*c* 1 in H_2O), and phenylosazone, m. p. 157—158°. We are also indebted to Dr. E. Percival for another sample.

(a) *Qualitative.* A solution of 4-*O*-methyl-D-fructose (2·20 g.) in oxygen-free water (100 ml.) was heated with calcium hydroxide (2 g.) on the boiling-water bath in a stream of nitrogen for 2 hr. After filtration the pale yellow solution was saturated with carbon dioxide, brought to the b. p., again filtered, and evaporated to dryness. Fractional precipitation of an aqueous solution of the residue (2·21 g., 98%) with ethanol yielded pure calcium α-D-gluco*iso*saccharinate which

Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography * G	F	S	Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography * G	F	S
0	+60·8°	0	10	—	—	48	−13°	0·33	3	4	1
0·5	+50	0	10	—	—	72	−11	0·46	2	3	2
1·0	+45	0	8	1	—	144	− 2	0·67	2	2	3
2·0	+38	0	7	2	—	221	− 2	0·75	1	1	4
3·0	+34	0	6	3	—	337	− 2	0·80	—	—	5
5·0	+27	0	5	5	—	485	− 2	0·83	—	—	5
7·5	+23	0·03	5	5	—	650	− 2	0·86	—	—	5
24	−11	0·16	4	5	—	805	− 2	0·89	—	—	5
31	−13	0·19	3	5	—						

* G = 4-*O*-methyl-D-glucose (R_F 0·48) (solvent a, sprays a, b). F = 4-*O*-methyl-D-fructose (R_F 0·55). S = saccharinic acid ($R_F < 0·05$). Numbers denote relative intensity of spots (10 maximum).

was converted into the corresponding brucine salt, m. p. and mixed m. p. 160—161°, and into the crystalline lactone, m. p. and mixed m. p. 94—96°. Later fractions from the precipitation of the calcium salts yielded calcium β-D-gluco*iso*saccharinate, from which was prepared the brucine salt, m. p. and mixed m. p. 190—195°, $[\alpha]_D^{20}$ −22·5° (*c* 2 in H_2O).

(b) *Quantitative.* A solution of 4-*O*-methyl-D-fructose (0·0790 g.) in oxygen-free 0·0393N-lime-water (25 ml.) was kept at 25° and the fall in alkalinity measured as described for 4-*O*-methyl-D-glucose. The change in optical rotation of the alkaline solution was observed in a separate experiment. Paper chromatography on intermediate samples was carried out as for 4-*O*-methyl-D-glucose (see Table); as also in that case no spot corresponding to 4-*O*-methyl-D-

Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography * F	G	P	S	Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography * F	G	P	S
0·25	−90°	0·03	10	—	—	—	24	−27°	0·35	5	1	1	2
0·5	−88	0·04	10	—	—	—	48	−16	0·48	4	1	1	2
1·0	−84·5	0·06	10	—	—	—	150	− 7	0·83	1	1	1	3
2·0	−81	0·08	10	—	—	—	240	− 2	0·91	—	—	—	3
4·5	−66·5	0·12	8	1	—	1	480	− 2	0·92	—	—	—	3
7·5	−56	0·16	7	1	1	1							

* F = 4-*O*-methyl-D-fructose (R_F 0·55) (solvent a, sprays a, b). G = 4-*O*-methyl-D-glucose (R_F 0·49). P = supposed 4-*O*-methyl-D-psicose (R_F 0·61). S = saccharinic acids ($R_F < 0·05$).

mannose was detected, but this does not exclude the possibility that a trace of this compound, probably having an R_F value very similar to that of 4-*O*-methyl-D-fructose, may be present.

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British Rayon Research Association, Heald Green Laboratories,
Wythenshawe, Manchester. [*Received, February 23rd,* 1955.]

Approximate Potential Function for the Out-of-plane Vibrations of Ethylene, and of Aromatic Molecules such as Benzene and Naphthalene.

By C. A. Coulson and S. Senent.

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An approximate potential function is described for the out-of-plane vibrations of π-electron systems such as ethylene, benzene, naphthalene, and higher aromatic fused-ring hydrocarbon molecules. The advantage of this potential function, which can be tested and shown to give good results for ethylene, benzene, and certain vibrations of naphthalene, is that it requires only two force constants.

Satisfactory potential functions exist to describe the out-of-plane vibrations of simple π-electron molecules such as ethylene and benzene. These enable us to define the potential energy in terms of the perpendicular displacements z_r of the atoms from their mean plane provided that the z_r are supposed to be small. With relatively small molecules only a few force constants are required. But with large molecules there are so many force constants in a complete potential function that we have little hope of determining them all. It is of interest, therefore, to devise a simple potential function which will deal reasonably with simple molecules and can also be used, without further analysis, for large ones. The succeeding paper illustrates one of the ways in which such a potential function may be used; by its aid we have calculated the deformation and strain energy in the overcrowded molecule 3 : 4-5 : 6-dibenzophenanthrene : other similar applications are in progress and will be reported in due course. The potential function which we shall describe here involves only two force constants. But it would not be difficult to give it greater flexibility by allowing different values to the same force constant when it arises (see below) in a different molecular environment. The present discussion, however, will be given entirely in terms of just two such constants. A particular case of our potential function has already been used by Bell (*Trans. Faraday Soc.*, 1945, **41**, 292) in studying out-of-plane vibrations in benzene.

Simplified Ethylene-type Potential.—Let us consider first the ethylene-type system represented in Fig. 1, in which the valency angles are all assumed to be 120°. There are 6 atoms 1 . . . . . 6, and our object is to express the potential energy V as a function $V(z_1 \ldots\ldots z_6)$ of their normal displacements z_r from the equilibrium plane of the molecule. For simplicity let us suppose that all five bond lengths are identical ($= a$). Later we shall remove this restriction. It is convenient to introduce M and M' (Fig. 1) which are the remaining vertices of the parallelograms shown. The lines 1–M and 2–M' bisect the angles 3–1–4 and 5–2–6 respectively. In equilibrium M and M' are in the plane of the whole molecule; but in the displaced configuration the displacements of M and M' are $z_3 + z_4 - z_1$ and $z_5 + z_6 - z_2$.

Let us suppose that we are given the molecule in its displaced configuration, having non-zero z_r. And let us calculate how much energy is recovered when the molecule is brought back to its initial condition with all $z_r = 0$. This may be achieved in four stages :

(i) A uniform displacement, $(z_1 + z_2)/2$, brings the centre of the molecule to its correct position. No work is done since the shape of the molecule is unchanged.

(ii) A uniform rotation through an angle $(z_1 - z_2)/a$ around the axis of symmetry perpendicular to the line 1–2 will bring atoms 1 and 2 into their correct positions. No work is done in this rigid-body rotation. The new co-ordinates of the four edge atoms are given by :

$$z'_3 = z_3 - \tfrac{1}{2}z_1 + \tfrac{1}{2}z_2, \text{ etc.}$$

(iii) Rotations around axes through atoms 1 and 2 will bring M and M' to their correct positions. The angle of twist around atom 1 will be $(z'_3 + z'_4)/a$, *i.e.*, $(z_3 + z_4 + z_2 - 3z_1)/a$. If we may suppose that the energies of these two deformations are additive, the energy recovered in this stage is

$$\tfrac{1}{2}k_1(z_2 + z_3 + z_4 - 3z_1)^2 + \tfrac{1}{2}k_1(z_1 + z_5 + z_6 - 3z_2)^2 \quad . \quad . \quad . \quad (1)$$

where k_1 is some force constant yet to be determined. Strictly, we should add to (1) a cross-term proportional to $(z_2 + z_3 + z_4 - 3z_1)(z_1 + z_5 + z_6 - 3z_2)$, since otherwise the in-phase and the out-of-phase flapping frequencies of ethylene would be governed by the same force constant. We know that this is not so. But fortunately the difference is not great, and we shall find that this term may be omitted without serious loss of accuracy. In view of our intention to obtain the simplest worthwhile potential function, we shall neglect this cross-term completely, though it may be inserted quite easily if we wish to do so.

(iv) At the end of stage (iii) the displacements of the atoms 3, 4, 5, 6 are given by $z_3'' = (z_3 - z_4)/2$, etc. A torsion of the group 3–1–4 around the axis 1–2 by an amount $2z_3''/a\sqrt{3}$ brings this end of the molecule into the required position. There is thus a total torsion in the bond 1–2 which amounts to $2(z_3'' + z_6'')/a\sqrt{3}$. An energy is recovered in the process, which is of the form

$$\tfrac{1}{2}h_2(z_3 - z_4 - z_5 + z_6)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The total potential energy $V(z_1 \ldots . z_6)$ is therefore the sum of the two expressions (1) and (2). We have already seen that (2) measures the torsion around the axis of the

FIG. 1.

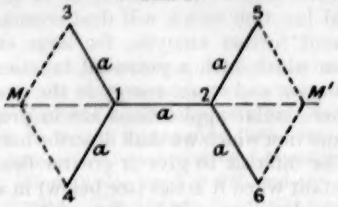


FIG. 2.

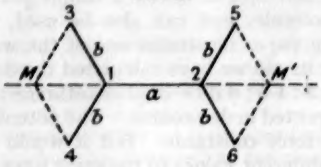


FIG. 3.

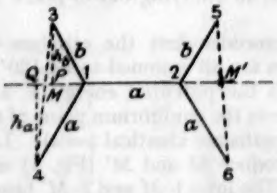
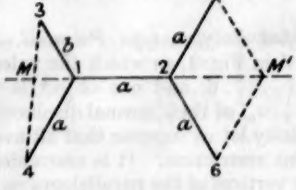


FIG. 4.



molecule; but (1) is also recognised to have a simple physical interpretation as arising from the lack of planarity of the atoms around 1 and 2. This is because, for example, $(z_2 + z_3 + z_4 - 3z_1)/3$ is precisely the distance by which atom 1 is separated from the plane containing atoms 2, 3, and 4. It is convenient to refer to (1) as the planarity terms and (2) as the torsion terms.

More General Ethylene-type Potential.—Formulæ (1) and (2) were obtained on the assumption that, as in Fig. 1, all the bond lengths were equal, with a value a. But it is not difficult to extend the analysis to cover the other cases with which we shall be concerned, represented by Figs. 2—4. Here certain of the "C–H type" bonds are supposed to have a different length b. The discussion, apart from the asymmetrical case in Fig. 3, is quite straightforward, and need not be reproduced in detail. In all cases the potential energy is the sum of planarity and torsion terms, though these are given by slightly more involved functions than in (1) and (2). They are:

$$\text{Planarity terms: Fig. 2,} \quad \tfrac{1}{2}k_1\left\{\frac{a}{b}z_3 + \frac{a}{b}z_4 + z_2 - \left(1 + \frac{2a}{b}\right)z_1\right\}^2$$

$$+ \tfrac{1}{2}k_1\left\{\frac{a}{b}z_5 + \frac{a}{b}z_6 + z_1 - \left(1 + \frac{2a}{b}\right)z_2\right\}^2 \quad . \quad . \quad . \quad (3)$$

Fig. 3, $\frac{1}{2}k_1\left\{\frac{a}{b}z_3 + z_4 + z_2 - \left(2 + \frac{a}{b}\right)z_1\right\}^2$

$+ \frac{1}{2}k_1\left\{\frac{a}{b}z_5 + z_6 + z_1 - \left(2 + \frac{a}{b}\right)z_2\right\}^2$ . . . . . (4)

Fig. 4, $\frac{1}{2}k_1\left\{\frac{a}{b}z_3 + z_4 + z_2 - \left(2 + \frac{a}{b}\right)z_1\right\}^2$

$+ \frac{1}{2}k_1\left\{z_5 + z_6 + z_1 - 3z_2\right\}^2$ . . . . . (5)

Torsion terms: Fig. 2, $\frac{1}{2}k_2\left\{z_3 - z_4 - z_5 + z_6\right\}^2$ . . . . . (6)

Fig. 3, $\frac{1}{2}k_2\left\{\frac{a}{b}z_3 - z_4 - \frac{a}{b}z_5 + z_6 + \left(1 - \frac{a}{b}\right)(z_1 - z_2)\right\}^2$. (7)

Fig. 4, $\frac{1}{2}k_2\left\{\frac{a}{b}z_3 - z_4 - z_5 + z_6 + \left(1 - \frac{a}{b}\right)z_1\right\}^2$ . . . (8)

The physical significance of these terms remains unchanged from what it was in the simpler cases (1) and (2). It should be noted that we have used the same force constants k_1 and k_2 in all the expressions (1)—(8). Strictly there should be four distinct k_1 and four distinct k_2. It would be possible to introduce all these. But we shall see that a surprisingly good approximation is obtained by giving all the k_1 constants the same value, and also all the k_2 constants.

Final Potential Function.—We are now in a position to write down the complete potential function for any of the molecules which are covered by this type of analysis. This is the sum of a planarity term for any atom around which there are three other bonded atoms, and a torsion term for any bond each of whose ends are attached to two other atoms. Thus for benzene (Fig. 5) there are six planarity terms for the carbon atoms, and six torsion terms for the carbon–carbon bonds. The planarity terms are of the same form as the first half of (4), the torsion terms are as in (7) where a denotes the C–C distance and b the C–H distance. In ethylene we have the situation of Fig. 2. In naphthalene (Fig. 6) there are two planarity terms of type (1) corresponding to $C_{(9)}$ and $C_{(10)}$; eight planarity terms as in benzene, corresponding to $C_{(1)} \ldots . C_{(8)}$; one torsion term (2) associated with $C_{(9)}$–$C_{(10)}$; four torsion terms (8) associated with $C_{(9)}$–$C_{(1)}$, $C_{(9)}$–$C_{(8)}$, $C_{(10)}$–$C_{(4)}$ and $C_{(10)}$–$C_{(5)}$; and six torsion terms (7) associated with the remaining carbon–carbon bonds. The potential energy function for any other molecule can be written down equally easily.

The only bonds around which torsion occurs are C–C bonds. The appropriate force constant k_2 would therefore be expected to vary with the degree of double-bond character, going from a very small value for near-single bonds to a maximum for the pure double bond of ethylene. In the aromatic molecules for which this analysis is chiefly intended, the variations in bond order are relatively small. This is the ground on which we justify a single value of k_2, except, of course, for ethylene where obviously a different and larger value will be needed.

The justification for a single planarity force constant k_1 is less convincing. However, apart from highly condensed molecules such as ovalene, the number of internal carbon atoms all of whose neighbours are other carbon atoms, is quite small. Most of the carbon atoms are secondary ones.* We might expect that there would be different k_1 values for primary, secondary, and tertiary atoms. Once again, therefore, with the exception of ethylene, we shall not introduce a great error in the planarity contributions to the total potential by treating all the carbon atoms as secondary, with a common value of k_1.

* The convention is adopted that a primary, secondary, or tertiary carbon atom is one which has one, two, or three adjacent carbon atoms within the π-electron framework of the molecule.

It is not difficult to relate our force constants to more conventional ones. A single example suffices. In benzene (Fig. 5) if we suppose that all the $z_r = 0$ except z_1, our potential energy function takes the form

$$\tfrac{1}{2}k_1\left(\frac{a}{b}z_1\right)^2 + \tfrac{1}{2}k_2\left(\frac{a}{b}z_1\right)^2 = \tfrac{1}{2}kz_1^2$$

where $k = (k_1 + k_2)a^2/b^2$. This constant k governs the separate flapping of a single C–H bond. Other correlations follow similarly. An advantage of our potential function is that it takes account of certain interactions between the flapping of nearby bonds, and the buckling of the carbon framework, in a particularly simple physical fashion.

Application to Ethylene.—The out-of-plane vibrations of ethylene have been studied very fully (*e.g.*, by Bernard and Manneback, *Ann. Soc. sci. Bruxelles*, 1939, **59**, 113; Arnett and Crawford, *J. Chem. Phys.*, 1950, **18**, 118; Herzberg, "Molecular Spectra and Molecular Structure, Vol. II, Polyatomic Molecules," Van Nostrand, New York, 1954, especially pp. 150, 183, 189). As Sutherland and Dennison (*Proc. Roy. Soc.*, 1935, *A*, **148**, 250) have shown, the out-of-plane vibrations require three force constants, and fall into the symmetry classes A_{1u}, B_{1u}, and B_{2g}. There is just one normal mode in each class. The A_{1u} mode is the internal torsion mode, B_{1u} represents flapping in phase, and B_{2g} flapping out of phase. The conventional numbering of these frequencies is ν_4, ν_7, and ν_8 respectively. Table 1 shows some of the assignments that have been made by various authors. If we take

TABLE 1. *Frequencies of out-of-plane vibrations in ethylene.*

		Frequency (cm.$^{-1}$)				
Symmetry	Label	(*a*)	(*b*)	(*c*)	(*d*)	Calc. frequency
A_{1u}	ν_4	825	—	950	1027	1027
B_{1u}	ν_7	949·2	949·2	949·2	950	889
B_{2g}	ν_8	950	—	943	943	1021

(*a*) Gallaway and Barker, *J. Chem. Phys.*, 1942, **10**, 88. (*b*) Thorndike, Wells, and Wilson, *ibid.*, 1947, **15**, 157. (*c*) Rasmussen and Brattain, *ibid.*, p. 120. (*d*) Arnett and Crawford, *ibid.*, 1950, **18**, 118.

1·34 and 1·08 Å for the C=C and C–H bond lengths, we find that the frequency ν_4 determines a unique value $k_2 = 0{\cdot}157 \times 10^5$ dyne cm.$^{-1}$. With only one remaining parameter we cannot satisfy both ν_7 and ν_8. Taking the mean of the two values of k_1 which would be required to give these two frequencies leads to a magnitude $k_1 = 0{\cdot}131 \times 10^5$ dyne cm.$^{-1}$, and calculated frequencies as shown in the last column of the Table. It is gratifying that the complete neglect of the cross-term in the potential function referred to on p. 1814 leaps to an error nowhere greater than 8%.

Application to Benzene.—The potential function for benzene has been studied by many writers, *e.g.*, Wilson (*Phys. Rev.*, 1934, **45**, 706), Manneback (*Ann. Soc. sci. Bruxelles*, 1935, **55**, *B*, 129, 237), Lord and Andrews (*J. Phys. Chem.*, 1937, **41**, 149), Duchesne and Penney (*Bull. Soc. Roy. Sci. Liège*, 1939, **8**, 514), Bell (*Trans. Faraday Soc.*, 1945, **41**, 293), Bak (*Kgl. Danske Vid. Sels. Mat. Phys. Medd.*, 1945, **28**, No. 9), Miller and Crawford (*J. Chem. Phys.*, 1946, **14**, 282; 1949, **17**, 249), and Ingold and his collaborators (*J.*, 1936, 971). The last three of these are the most complete, but they require no less than eight force constants to deal with the out-of-plane vibrations. These vibrations have total symmetry $A_{2u} + 2B_{2g} + 2E_{2u} + 2E_{2g}$. Ingold and his collaborators (*loc. cit.*) assign these to the frequencies ν_{11}, ν_4, ν_5, ν_{16}, ν_{17}, and ν_{10} as in Table 2.

We have used the potential function, with only two parameters, as described earlier. The bond lengths were taken to be 1·40 Å (C–C) and 1·08 Å (C–H). We used the two frequencies ν_{10} and ν_{11} to determine the appropriate values of k_1 and k_2, and found them to be $k_1 = 0{\cdot}1474 \times 10^5$ dyne cm.$^{-1}$, $k_2 = 0{\cdot}0553 \times 10^5$ dyne cm.$^{-1}$. The remaining four frequencies shown in the last column of Table 2 followed from these values of k_1 and k_2. It is most gratifying to see that the accuracy thus obtained is of the same order as in ethylene.

Indeed, if we had chosen k_1 and k_2 to give the best all-round agreement, instead of the correct values of ν_{10} and ν_{11}, we could doubtless have done better than in Table 2.

TABLE 2. *Frequencies (cm.$^{-1}$) for benzene vibrations.*

		Wave-number				
Symmetry	Label	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)
A_{2u}	ν_{11}	671	671	668	671	(671)
B_{2g}	ν_4	—	664	638	685	638
	ν_5	1000	1048	1060	993	1110
E_{2u}	ν_{16}	—	406	403	404	413
	ν_{17}	890	845	873	985	1049
E_{1g}	ν_{10}	849	950	858	850	(850)

(*a*) Angus, Bailey, Hale, Ingold, Leckie, Raisin, Thompson, and Wilson, *J.*, 1936, 971. (*b*) Langseth and Lord, *Kgl. danske, Vid. Sels. Mat.-fys. Medd.*, 1938, **16**, No. 6. (*c*) Bak, *ibid.*, 1945, **28**, No. 9. (*d*) Crawford and Miller, *J. Chem Phys.*, 1946, **14**, 282. (*e*) Calc. in present paper. Figures in parentheses were used to fix parameters k_1 and k_2.

A word needs to be said concerning our use of the C–C bond distance 1·40 Å. We have chosen this value rather than the recent *X*-ray value of 1·375 Å (Cox and Smith, *Nature*, 1954, **173**, 75) because it has recently been confirmed in accurate high-dispersion Raman studies by Stoicheff (*Canad. J. Phys.*, 1954, **32**, 339). A satisfactory decision between these two divergent values does not seem possible at present. We have preferred the

FIG. 5. *Numbering of atoms in benzene.*

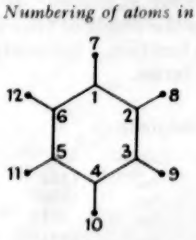
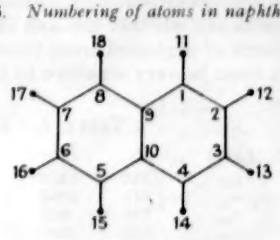


FIG. 6. *Numbering of atoms in naphthalene.*



Raman value both because it relates to the molecule in the gas phase and because it is essentially spectroscopic. Our comparisons with experiment must also be wholly spectroscopic.

Before leaving benzene, it is interesting to compare our values of k_1 and k_2 and the associated force constant k (p. 1816) for displacement of a single H atom, with the value calculated in the detailed work of Miller and Crawford (*J. Chem. Phys.*, 1946, **14**, 282) where this particular constant is called A. We find a value $k = 0{\cdot}340 \times 10^5$ dyne cm.$^{-1}$, whereas Miller and Crawford obtain a value $A = 0{\cdot}378 \times 10^5$ dyne cm.$^{-1}$. The agreement is satisfactory. It is also satisfactory that the torsion force constant k_2 for benzene is distinctly smaller than that for ethylene.

Application to Naphthalene.—The complete potential function for naphthalene (Fig. 6) is not known, nor are complete and final assignments made for all the fundamental frequences. Our approach to this molecule must therefore be different from that for ethylene and benzene where all the frequencies were known and an agreed assignment exists. There are 15 out-of-plane modes of vibration belonging to the representation $4A_u + 4B_{1u} + 3B_{2g} + 4B_{3g}$ of the symmetry group D_{2h}. The A_u type are inactive in both infra-red and Raman spectra, B_{1u} are active in both, B_{2g} and B_{3g} are active in Raman only. The assignments of these fifteen frequencies to the four symmetry classes have varied from one writer to another (cf., *e.g.*, Pimentel and McClellan, *J. Chem. Phys.*, 1952, **20**, 270; Manneback, *J. Chim. phys.*, 1949, **46**, 49; Barrow and McClellan, *J. Amer. Chem. Soc.*, 1951, **73**, 573) but the most satisfactory solution appears to be that of McClellan and Pimentel (in the press; we acknowledge the kindness of the authors in providing us with an advance copy of the manuscript) who studied both $C_{10}H_8$ and $C_{10}D_8$, and attempted a full

allocation of all the 48 fundamental frequencies of these two molecules. In this allocation only the B_{1u} group seems completely reliable: the difficulties associated with a search for the four inactive A_u frequencies are obviously great. For that reason the comparison with experiment shown in Table 3 must be treated with some reserve, apart from the B_{1u} group of frequencies.

In making our calculations we have used the potential function described on p. 1815, with only two force constants. We have taken the bond lengths to be the same in naphthalene as in benzene (Coulson, Daudel, and Robertson, *Proc. Roy. Soc.*, **1951**, *A*, **207**, 306) and have therefore adopted the numerical values of k_1 and k_2 previously obtained from benzene. It is worth mention, therefore, that no empirical quantities whatever for naphthalene are used in the calculations of the last column in this Table. Without doubt we could have improved the agreement for the important B_{1u} vibrations, while still adhering to only two distinct force constants, if we had been prepared to modify the benzene values of k_1 and k_2. Further, by using two separate k_1 and k_2 for the secondary and the tertiary carbon atoms, we could have done better still. We have not done this because our object in this paper is to show how good a potential function can be found for this—and larger—molecules by the simple expedient of carrying-over the two force constants for benzene. The agreement for the B_{1u} vibrations in $C_{10}H_8$ is within 10%, a situation which seems to us eminently satisfactory both in showing that the potential function is good and also in confirming the experimental assignments. The agreement for the higher frequencies in the B_{2g} and B_{3g} classes is only a little worse than for the B_{1u} class. But the lower frequencies are less satisfactory, and so are the more difficult A_u modes. It is not possible at this stage to say whether the lack of agreement here is the result of false assignments or the importance of neglected cross-terms in the potential function. Certainly the very low frequencies must be very sensitive to the values of such terms.

TABLE 3. *Frequencies in naphthalene.*

Symmetry	Label	(*a*)	(*b*)	(*c*)	Symmetry	Label	(*a*)	(*b*)	(*c*)
A_u	ν_{10}	1146	1307	1143	B_{3g}	ν_{26}	1254	1167	1040
	ν_{11}	841	1094	917		ν_{27}	1168	715	722
	ν_{12}	726	842	549		ν_{28}	191	191	365
	ν_{13}	586	(400)	222	B_{3u}	ν_{37}	1624	1099	1107
B_{1u}	ν_{23}	949	956	1053		ν_{38}	972	774	937
	ν_{23}	821	780	776		ν_{39}	742	588	687
	ν_{24}	747	475	422		ν_{40}	406	285	436
	ν_{25}	80	176	183					

(*a*) Barrow and McClellan, *loc. cit.* (*b*) McClellan and Pimentel, in the press. (*c*) Calc. in the present paper.

In conclusion, we believe that our simple potential function should be useful for more complicated molecules such as anthracene or pyrene, or the dibenzophenanthrene discussed in the following paper. We also, once more, thank Drs. A. L. McClellan and G. C. Pimentel for valuable correspondence and information concerning the experimental assignments of frequencies in naphthalene.

MATHEMATICAL INSTITUTE, OXFORD.
LABORATORIO DE QUÍMICA FÍSICA,
SECCION DEL INSTITUTO "A. DE G. ROCASOLANO," DEL C.S.I.C.,
VALLADOLID, SPAIN.

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Molecular Deformation in 3 : 4-5 : 6-*Dibenzophenanthrene.*

By C. A. Coulson and S. Senent.

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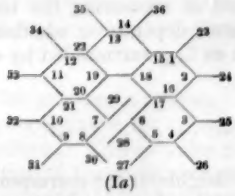
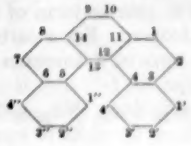
Steric limitations prevent the molecule 3 : 4-5 : 6-dibenzophenanthrene from being planar. On the basis of a plausible potential function for out-of-plane displacements of the various atoms, the molecular deformation is calculated. Excellent agreement with McIntosh, Robertson, and Vand's experimental values is obtained. The loss of resonance energy as a result of the deformation is estimated to be 18 kcal. mole^{-1}. The total strain energy may be about 28 kcal. mole^{-1}.

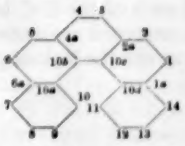
Recently one of us (Senent, *Anales Real Soc. Esp. Fís. Quím.*, 1954, **50**, *B*, 337) calculated bond orders and resonance energy for 3 : 4-5 : 6-dibenzophenanthrene (I) by the method of molecular orbitals. As then stated a proper study of this molecule requires (*a*) the determination of its molecular diagram, on the hypothesis that it is planar, followed by (*b*) a study of its deformation. As shown, there is serious overcrowding between the hydrogen atoms numbered 28 and 29, and also between the carbon atoms numbered 6 and 7. It is generally found that non-bonded carbon atoms do not approach closer than 3·0 Å, and that the shortest hydrogen–hydrogen distances in aliphatic hydrocarbon crystals (see, *e.g.*, the accurate electron-diffraction values of B. K. Weinstein and Z. G. Pinsker, 3rd Internat. Congr. Crystall., Moscow, 1954, **10**, 154) are 2·49—2·50 Å. Now if the hexagons are approxi-



(I*a*)



(I*b*)



(I*c*)

(*a*) Numbering used in this paper. This numbering was chosen for convenience in description and mathematical analysis.
(*b*, *c*) Standard organic chemical numberings (cf. Table).

mately regular, the distance $C_{(6)}$–$C_{(7)}$ will be about 1·4 Å, so that all four atoms $C_{(6)}$, $C_{(7)}$, $H_{(28)}$, $H_{(29)}$ in this region are well within the forbidden distances, if the molecule is assumed to be planar. It is clear that since $C_{(6)}$ and $C_{(7)}$ are too close together, no bending of the bonds 6–28, 7–29 will remove the overcrowding. It is also clear that although this overcrowding could be relieved in principle by splaying-out the two "legs" of the molecule in such a way that the system remained coplanar, this would involve considerable changes in bond lengths and bond angles. Some similar calculations for diphenyl by Longuet-Higgins and Coulson (briefly reported by Coulson in "Quantum-Mechanical Methods in Valence Theory," Office of Naval Research, U.S.A., 1951, p. 42) suggest that this type of relief of steric strain requires a good deal more energy than if it is achieved by buckling the molecule out of a plane. A buckled shape has in fact recently been discovered experimentally by McIntosh, Robertson, and Vand (*Nature*, 1952, **169**, 322; *J.*, 1954, 1661). It is reasonable, therefore, to suppose that the overcrowding in (I) is relieved by displacements of the various C and H atoms in a direction normal to the original undisturbed molecular plane. This is the model adopted in the present paper. It is supported by the three-dimensional diagram of the molecule shown in Fig. 5 of the paper by McIntosh *et al.* We shall show that by a simple application of the potential function for perpendicular displacements of the atoms of an aromatic hydrocarbon molecule, described in the preceding paper, it is possible to predict the details of the out-of-plane distortion with excellent fidelity. At the same time an estimate is obtained of the loss of resonance energy as a result of the deformation.

Let us take the plane of the undistorted molecule as the plane $z = 0$, and suppose that in the distortion the atom r is displaced a perpendicular distance z_r. The resulting changes in bond lengths and angles are of the second order of small quantities, and may therefore be neglected, unless the z_r fluctuate rapidly from atom to atom. We further suppose that these displacements are the only ones which take place. The potential energy of the deformed molecule will be a function $V(z_1, \ldots z_{36})$ of the co-ordinates z_r. Presumably the equilibrium values of the z_r will be such as minimise V subject to the van der Waals constraints in the region of atoms 6, 7, 28, and 29. In order to proceed further, therefore, we must discuss (*a*) the analytical form of V, and (*b*) the limiting values of z_6, z_7, z_{28}, and z_{29}.

It is shown in the paper which precedes this that a satisfactory potential function can be devised, which will account for the out-of-plane vibration frequencies in ethylene, benzene, and naphthalene with the use of only two distinct force constants. Now the C–C and C–H bonds in our present molecule must evidently resemble those of benzene and naphthalene quite closely. We may therefore adopt this potential function and use it to define V. Better agreement with experiment could no doubt be obtained if we chose a larger number of force constants, or even different values from those estimated from benzene; but we shall be able to show that by adopting these values we are led to an excellent agreement with the experimentally measured deformation. And our calculations have the advantage of making no appeal to any experimental results other than the fundamental frequencies of benzene, and the van der Waals radii of carbon and hydrogen. According to this theory $V(z_1 \ldots z_{36})$ may be regarded as the sum of two sets of terms. The first set measures the lack of planarity of the three bonds around every carbon atom in the skeleton of the molecule; the second set may be interpreted as measuring the torsion around each of the C–C bonds. The precise form of these terms depends on whether the atoms concerned are carbon or hydrogen. For a carbon such as $C_{(19)}$ surrounded by other carbon atoms the lack-of-planarity term in V amounts to

$$\tfrac{1}{2}k_1\left\{z_{18} + z_{20} + z_{22} - 3z_{19}\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

For a carbon atom such as $C_{(14)}$ which has one hydrogen as neighbour the corresponding term involves the C–C and the C–H distance (a and b respectively). It is

$$\tfrac{1}{2}k_1\left\{\frac{a}{b}z_{36} + z_{15} + z_{13} - \left(2 + \frac{a}{b}\right)z_{14}\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

For a bond such as $C_{(18)}$–$C_{(19)}$ entirely surrounded by other carbon atoms, the torsion term is

$$\tfrac{1}{2}k_2\left\{z_{15} - z_{17} + z_{20} - z_{22}\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

For a bond such as $C_{(1)}$–$C_{(15)}$ where there is one neighbouring hydrogen atom, the torsion term is

$$\tfrac{1}{2}k_2\left\{\frac{a}{b}z_{23} - z_2 + z_{18} - z_{14} + \left(1 - \frac{a}{b}\right)z_1\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Finally, for a bond such as $C_{(1)}$–$C_{(2)}$ surrounded by two hydrogen atoms, the torsion term is

$$\tfrac{1}{2}k_2\left\{\frac{a}{b}z_{24} - z_{16} + z_{15} - \frac{a}{b}z_{23} + \left(1 - \frac{a}{b}\right)(z_2 - z_1)\right\}^2 \quad . \quad . \quad . \quad . \quad (5)$$

The complete expression for V is the sum of terms (1)—(5) for each carbon atom and for each carbon–carbon bond. There are altogether 48 such squared terms. The appropriate numerical values of the parameters are:

$$a = 1{\cdot}40 \text{ Å}, \; b = 1{\cdot}08 \text{ Å}, \; k_1 = 0{\cdot}1474 \times 10^5 \text{ dynes cm.}^{-1},$$
$$k_2 = 0{\cdot}0551 \times 10^5 \text{ dynes cm.}^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

We have still to discuss the displacements z_6, z_7, z_{28}, z_{29}. Viewed along the molecular plane in the direction of the axis of symmetry the overcrowded region must resemble Fig. 1, in which the horizontal line represents the undistorted molecule, and in which one half of the molecule has been deflected above the original plane, and the other half below it. The $C_{(6)}$–$C_{(7)}$ distance is found by McIntosh *et al.* to be 3·0 Å. This value is about the shortest carbon–carbon distance found in organic molecules, and is identical with the corresponding distance in 3 : 4-benzophenanthrene, recently studied by Herbstein and Schmidt (*J.*, 1954, 3302). It suggests that we may take the van der Waals radius of carbon in this somewhat compressed system as 1·5 Å. We should then expect the $C_{(7)}$–$H_{(28)}$ distance to be about 1·5 + 1·2 = 2·7 Å. Now the undistorted $C_{(6)}$–$C_{(7)}$ distance, represented by A–B in Fig. 1, will be about 1·4 Å, and the $C_{(6)}$–$H_{(28)}$ and $C_{(7)}$–$H_{(29)}$ bond lengths are 1·08 Å. Simple trigonometry shows that under these conditions $z_6 = -z_7 = 1{\cdot}32$ Å, $z_{28} = -z_{29} = 1{\cdot}36$ Å. These are the final values which we have adopted.

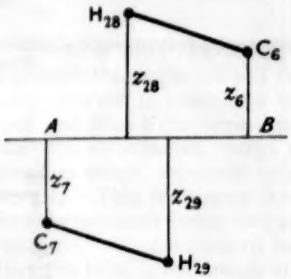


FIG. 1. *The overcrowded region.*

Our problem is now very simple : it is to find the minimum value of $V(z_1 \ldots . z_{36})$ with the above values for z_6, z_7, z_{28}, and z_{29}. We must therefore put $\partial V/\partial z_r = 0$ for all the remaining z_r. This provides us with a set of 32 linear equations. But the set reduces to 16 on account of the molecular symmetry according to which the right half of (I) is displaced upwards and the left half symmetrically downwards. The values of z_r which satisfy these conditions are shown in the Table, all displacements being measured in Å. It will be noticed that

Calculated and experimental displacements (values in parentheses are assumed).

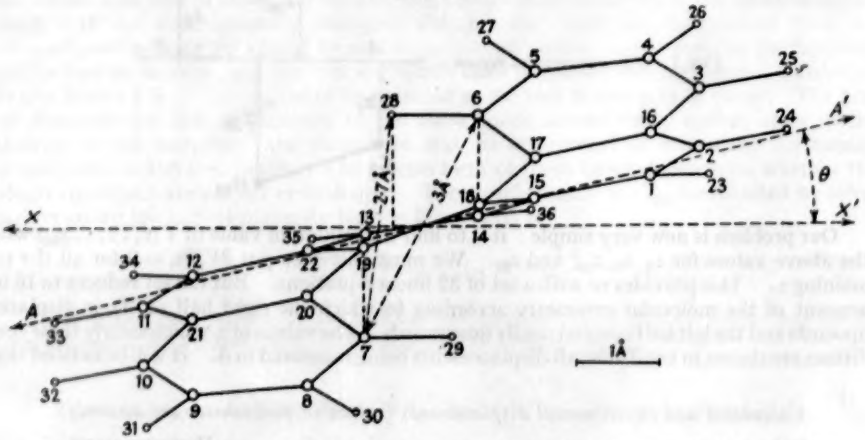
Carbon atoms numbered according to							Hydrogen atoms numbered according to			
(I*a*)	(I*b*)	(I*c*)	z_r	$z_r - \theta\rho_r$	Expt.	Δr	(I*a*)	(I*b*)	(I*c*)	z_r
1	1	2	$0{\cdot}63_0$	−0·07	−0·15	−0·08	23	1	2	$0{\cdot}61_7$
2	2	1	$1{\cdot}95_2$	0·09	0	−0·09	24	2	1	$1{\cdot}16_9$
3	1′	14	$1{\cdot}62_9$	0·80	0·78	−0·02	25	1′	14	$1{\cdot}79_5$
4	2′	13	$1{\cdot}96_3$	1·31	1·45	0·14	26	2′	13	$2{\cdot}36_6$
5	3′	12	$1{\cdot}85_0$	1·53	1·71	0·18	27	3′	12	$2{\cdot}19_2$
6	4′	11	(1·32)	1·15	1·20	0·05	28	4′	11	(1·36)
14	10	3	$0{\cdot}11_8$	−0·06	−0·16	−0·10	36	10	3	$0{\cdot}20_0$
15	11	2*a*	$0{\cdot}33_3$	0·03	0·02	−0·01				
16	3	14*a*	$1{\cdot}12_5$	0·43	0·40	−0·03				
17	4	10*d*	$0{\cdot}85_2$	0·48	0·55	0·07				
18	12	10*c*	$0{\cdot}27_4$	0·09	0·20	0·11				

some of these displacements are quite large, of the order of 2 Å. But since the displacements of different atoms vary smoothly from atom to atom, the apparently large displacements do not destroy the validity of our potential function.

Fig. 2 shows the displaced molecule, according to our calculations, when viewed along the original molecular plane. Comparison of this with Fig. 5 in the paper by McIntosh, Robertson, and Vand shows that our description is qualitatively correct. However the accuracy is almost quantitative, as may be seen as follows. It is not possible, from the *X*-ray analysis, to tell which would have been the basic plane from which we have measured

our z-displacements. But Professor Robertson has been kind enough to draw what he calls a medium plane through the molecule, and has measured the perpendicular displacements of the carbon atoms from this plane. (We cannot yet say anything about the hydrogen atoms, which are not experimentally resolved: our comparisons therefore are solely for the positions of the carbon atoms.) Trial-and-error suggests that the plane which Robertson has chosen for this purpose is defined by its trace A–A' in Fig. 2, the common line of this plane and the basic plane X–X' being the two-fold axis of symmetry of the molecule. We must therefore convert our z_r-values into corresponding displacements from A–A' instead of from X–X'. To the accuracy which is warranted by our whole analysis this may be achieved by replacing z_r by $(z_r - \theta\rho_r)$, where θ = angle between A–A' and X–X', and ρ_r is the axial distance of atom C_r from the axis of symmetry. These "reduced displacements" are also shown in the Table, where they are compared with the experimental values. The differences Δ_r shown are all satisfactorily small. When it is recalled that Robertson estimates his accuracy as of the order 0·1 to 0·2 Å, the agreement is all that

FIG. 2. *The dibenzophenanthrene molecule when projected in a direction perpendicular to the axis of symmetry.*



The figures denote the numbers (r) of the atoms and the small circles show their calculated displacements (z_r). θ = 0·24 radian.

could be desired; for the maximum Δ_r is only 0·18 Å, and the mean Δ_r is only 0·08 Å. The numerical value of θ to give the best fit has been taken to be 0·24 radian (13° 45′).

The agreement represented in the Table is almost too good; for the molecular-orbital calculations of Senent (*loc. cit.*) show that the bond orders of the outer, or exposed, bonds $C_{(12)}$–$C_{(14)}$, $C_{(1)}$–$C_{(2)}$, $C_{(3)}$–$C_{(4)}$, $C_{(11)}$–$C_{(12)}$, and $C_{(9)}$–$C_{(10)}$ are all rather larger than the average benzene order (**1·746, 1·764, 1·764, 1·710, 1·710,** respectively, to be compared with benzene **1·667**). This will lead to a shortening of these bonds, and therefore to a partial opening-out of the molecule, within its own molecular plane. As a result the distance A–B in Fig. 1 is likely to be rather greater than the value 1·40 Å which we assumed on the basis of five regular hexagons. This would tend to reduce the magnitudes of the displacements z_r which were needed to relieve the overcrowding. It seems likely that the chief effect of all this would be to diminish all calculated z_r in such a way that the angle θ was reduced without an equivalent decrease in the "reduced displacements." But in no case should we expect this effect to be large, and it is not possible to deal with it properly until the experimental values of the bond lengths have been determined with greater precision than at present.

We can use the z_r values of the Table to estimate the energy of deformation. This will

consist of two parts: the van der Waals repulsive overlap energy due to the closeness of the four overcrowded atoms $C_{(6)}$, $C_{(7)}$, $H_{(28)}$, and $H_{(29)}$, together with the energy required to distort the molecular framework. The second of these energies is identical with the loss of π-electron resonance energy and the energy of bending the σ-electron bonds. It is measured by the value of $V(z_1 \ldots\ldots z_{36})$ when we substitute the equilibrium values of the z_r. Now since V is a homogeneous polynomial of degree 2, it follows that

$$\sum_1^{36} z_r \frac{\partial V}{\partial z_r} = 2V$$

In equilibrium all $\partial V/\partial z_r = 0$ except for the four overcrowded atoms. Thus the energy of distortion is given quite simply by

$$z_6 \frac{\partial V}{\partial z_6} + z_{28} \frac{\partial V}{\partial z_{28}}$$

This amounts to 0·77 ev = 17·9 kcal. mole^{-1}. The first of the strain-energy terms is less easy to estimate, for we know practically nothing about the magnitudes of these repulsive forces between non-bonded atoms. Since they are believed to come into operation very suddenly as the internuclear separation is reduced, and then to increase rapidly, it seems probable that they will contribute rather less than the deformation energy terms; for if the repulsive terms were larger than the deformation terms, we could reduce the total strain energy by increasing the atomic displacements. This is because the deformation energy varies only as the square of the z_r values, but the repulsive forces vary as some higher power such as the inverse twelfth power of the distance. We are inclined to think that a value of the order of 10 kcal. mole^{-1} is likely. Then the total strain energy would be about 28 kcal. mole^{-1} and the resonance energy for the molecule (calculated by Senent, *loc. cit.*, to have the value 162 kcal. mole^{-1}) would have to be reduced by this amount. In view of our ignorance of the magnitude of the repulsive forces, no great reliance should be placed on this value. But it is likely to be correct as regards order of magnitude. The fact that it is so small in relation to the deformations z_r shows how relatively easy it is to build up quite large displacements in aromatic molecules of this sort by a series of small distortions around each of the carbon atoms of the molecular framework.

We acknowledge with great thanks much helpful correspondence with Professor J. M. Robertson, and also his kindness in providing us with the observed displacements for the Table.

Mathematical Institute, Oxford.

Laboratorio de Química Física,
Seccion del Instituto "A. de G. Rocasolano" del C.S.I.C.,
Valladolid, Spain.

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The Activation of Carbon–Carbon Double Bonds by Cationic Catalysts. Part I. The Dimerization of 1 : 1-*Diphenylethylene.*

By Alwyn G. Evans, N. Jones, and J. H. Thomas.

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The dimerization of 1 : 1-diphenylethylene to 1 : 1 : 3 : 3-tetraphenylbut-1-ene and the reverse reaction have been followed dilatometrically, with trichloroacetic acid as catalyst and benzene as solvent. The forward and the reverse reaction proceed to an equilibrium in which monomer and dimer are present, the same equilibrium being reached from either direction. The rate-determining step for the dimerization is the reaction of a monomer ion with a monomer molecule. The rate-determining step for the reverse reaction is the breakdown of a dimer ion. The formation of the monomer ion and the dimer ion involves three trichloroacetic acid molecules, one of which donates the proton to the olefin, the other two contributing to the solvation of the ion pair so formed.

The activation energies of the forward and the reverse reaction have been determined, and the heat of reaction has been obtained from the variation of the equilibrium constant with temperature.

It has been shown that unless a cocatalyst, *e.g.*, water, is present *iso*butene is not polymerized by boron trifluoride (A. G. Evans and Polanyi, *J.*, 1947, 252; A. G. Evans and Meadows, *Trans. Faraday Soc.*, 1950, **46**, 327) or by titanium tetrachloride (Plesch, Polanyi, and Skinner, *J.*, 1947, 257). In the presence of water the olefin is activated by accepting a proton from the chloride–water complex (for references see A. G. Evans, *J. Appl. Chem.*, 1951, **1**, 240). To investigate further this type of double-bond activation we have studied dilatometrically the reaction of 1 : 1-diphenylethylene in benzene when catalysed by trichloroacetic acid. Cationic catalysts bring about dimerization of this olefin (Schoepfle and Ryan, *J. Amer. Chem. Soc.*, 1930, **52**, 4021), polymerization to products of higher molecular weight being sterically impossible because of the bulky phenyl groups. Thus this reaction is very suitable for investigations of the mechanism by which cationic catalysts activate carbon–carbon double bonds.

Experimental

Materials.—Trichloroacetic acid (from B.D.H.) was purified by two distillations in a high vacuum, collected under a high vacuum and stored in sealed ampoules.

1 : 1-Diphenylethylene (from Messrs. Mersey Chemicals Ltd.) was distilled under reduced pressure through a 25-cm. point column, then distilled from potassium hydroxide pellets in a one-piece all-glass apparatus under a high vacuum.

1 : 1 : 3 : 3-Tetraphenylbut-1-ene was obtained by dissolving 1 : 1-diphenylethylene in glacial acetic acid containing a few drops of concentrated sulphuric acid. The dimer gradually crystallized and was filtered off, washed with acetic acid, drained, and recrystallized from dry light petroleum (b. p. 60—80°). Excess of solvent was removed by pumping out the fused material for several hours in a high vacuum. The final sample had m. p. 113° (cf. Schmitz-Dumont, Thomke, and Diebold, *Ber.*, 1937, **70**, 175).

Benzene, of "AnalaR" grade, was shaken with "AnalaR" concentrated sulphuric acid, then washed with distilled water, dried ($CaCl_2$, then Na wire), and fractionated through a 40-cm. point column. As used it had b. p. 79·5—80·0°.

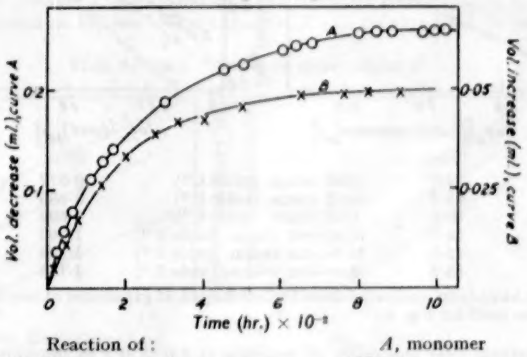
Procedure.—The dilatometers consisted of glass bulbs of about 30 ml. capacity fused to capillary stems on which volume changes could be read to ±0·001 ml. Reactions were carried out at about 35°, 45°, and 55°, the temperature being maintained by water-filled thermostats controlled to within ±0·05°. A master solution of trichloroacetic acid in benzene was made up by breaking a weighed ampoule of the acid under benzene, making the solution up to 100 ml. with benzene, and weighing the dried ampoule glass. The acid solutions of the olefin in benzene were obtained by adding a known fraction of this master solution to a known quantity of the olefin, and the resulting solution was made up to 100 ml. with benzene and introduced into a dilatometer, partially immersed in the thermostat. The dilatometer was then sealed and

totally immersed in the thermostat, and the volume of the solution observed at appropriate times. The concentrations of the reactants were chosen so that no appreciable volume change could occur in the time required to make up the solution, fill the dilatometer, and bring the system to the temperature of the thermostat. Some experiments in which the solution was completely freed from air on the high-vacuum line by repeated cooling and pumping out gave results identical with those carried out as described above.

Results

Dimerization of 1 : 1-*Diphenylethylene.*—(i) *Analysis of products.* The volume of the diphenylethylene–trichloroacetic acid–benzene mixture decreased gradually to constancy. In the absence of acid no change was detected during several weeks. An example of the plots obtained for volume decrease against time is shown in Fig. 1, curve *A*. After the reaction the dilatometer

Fig. 1. *Volume change during reaction at* 33·8°.



Reaction of :	*A*, monomer	*B*, dimer
Initial vol. (ml.) of solution	22·78	24·37
Initial concn. (mole l.$^{-1}$)	1·142 (monomer)	0·5555 (dimer)
Initial acid concn. (mole l.$^{-1}$)	0·709	0·768

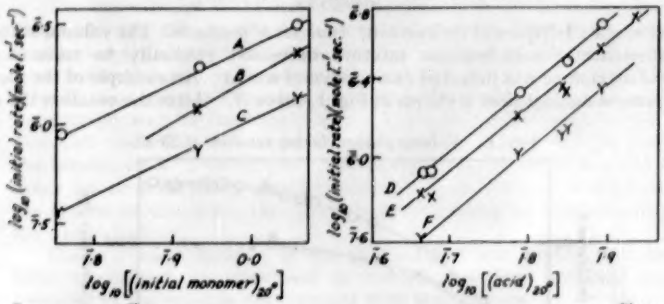
was broken and the trichloroacetic acid extracted in water and estimated by titration with alkali: no change in the acid concentration ever occurred. The benzene was removed from the non-aqueous layer by pumping in a high vacuum, and the residue was washed with methanol to remove unchanged 1 : 1-diphenylethylene, leaving crystals, m. p. 113° unchanged on crystallization from light petroleum (b. p. 60—80°); the material was thus established as 1 : 1 : 3 : 3-tetraphenylbut-1-ene. This also established that the dimer, 1-methyl-1 : 3 : 3-triphenylindane (which is produced from 1 : 1-diphenylethylene under certain conditions; Schoepfle and Ryan, *loc. cit.*) was not formed in our experiments, since this is very much less soluble in benzene and has m. p. 143°.

The dimer formed was less than corresponded to complete reaction. This was further investigated as follows. Solutions of monomer in benzene, and of dimer in benzene, were made up, the same weight of olefin being added to the same volume of benzene in each case. The densities of these two solutions were measured at different temperatures. From the difference in the densities, the volume change was determined for the complete conversion from monomer to dimer for a given concentration and at a given temperature. A more accurate method of measuring this volume change in the presence of the acid was developed when the order of the reaction was known. This method, described below, gave the following values for the conversion of one mole of monomer into dimer: 11·85 ml. at 33·8°, 11·70 ml. at 45·7°, and 12·57 ml. at 54·7°. These agree within 4% with those obtained from the density measurements. The percentage reaction calculated, by assuming a linear relation for the change of volume with conversion of monomer into dimer, was the same as that obtained from the analysis of the products at equilibrium. For example, for the reaction shown in Fig. 1, curve *A*, the amount of dimer present at the end of the reaction was found to be 0·483 mole/l. by the volume change method and 0·465 mole/l. by the analysis of the products. Thus the reaction proceeds to an equilibrium position, in which the only dimer present is 1 : 1 : 3 : 3-tetraphenylbut-1-ene. This point was completely established, as described below, by experiments on the reverse reaction.

(ii) *Analysis of reaction curves.* Because the reaction does not go to completion, we analysed the rate curves by obtaining the initial rate of the reaction from the initial slope. This method is quite accurate in these experiments since the reactions are slow.

(iii) *Orders in monomer and in acid.* The dependence of the initial rate on initial monomer concentration (at constant acid concentration), and on acid concentration (at constant initial monomer concentration), are given in Figs. 2*a* and *b* respectively for different temperatures.

FIGS. 2*a* and *b*. *Orders in monomer and acid.*



Curve	Temp.			Slope
A	54·7°	Acid concn. (mole l.$^{-1}$)	0·677	1·85
B	45·7	Acid concn. (mole l.$^{-1}$)	0·685	2·2
C	33·8	Acid concn. (mole l.$^{-1}$)	0·692	1·9
D	54·7	Monomer concn. (mole l.$^{-1}$)	1·092	3·12
E	45·7	Monomer concn. (mole l.$^{-1}$)	1·108	3·10
F	33·8	Monomer concn. (mole l.$^{-1}$)	1·121	3·15

Concentrations have been evaluated from the coefficient of expansion of benzene (Int. Crit. Tables, Vol. VI, p. 85), also used for Fig. 4.

We find by this method that the order of reaction is 2·0 ± 0·2 in monomer and 3·1 ± 0·1 in acid.

(iv) *Temperature-dependence.* Fig. 2 contains all the data required to yield the temperature dependence of the initial rate at constant acid and constant initial monomer concentration. A typical result is given in Fig. 3. The average value of the activation energy for the forward reaction obtained from plots of this type is 9·1 ± 0·5 kcal./mole.

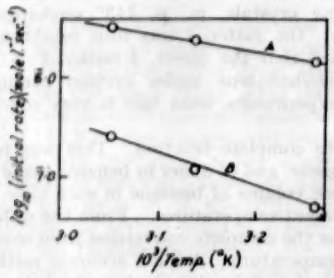


FIG. 3. *Temperature-dependence of initial rates.*
A, Dimerization reaction.
B, Reverse reaction.

Formation of Monomer from 1 : 1 : 3 : 3-*Tetraphenylbut*-1-*ene in Benzene.*—(i) *Analysis of products.* The volume of tetraphenylbut-1-ene–trichloroacetic acid–benzene systems increased gradually to constancy, as exemplified in Fig. 1, curve *B*. In the absence of acid no change in volume could be detected during several weeks. After reaction, the system was analysed in the same way as for the forward reaction: again no change in acid content was observed, and the amount of 1 : 1 : 3 : 3-tetraphenylbut-1-ene recovered (m. p. 113°) corresponded with that calculated from the observed volume change. For example, at 33·8° the amount of 1 : 1 : 3 : 3-tetraphenylbut-1-ene at equilibrium was 0·357 mole/l. by analysis, and 0·342 mole/l. by estimation from the volume change. This again establishes that none of the dimer, 1-methyl-1 : 3 : 3-triphenylindane, is formed in our experiments.

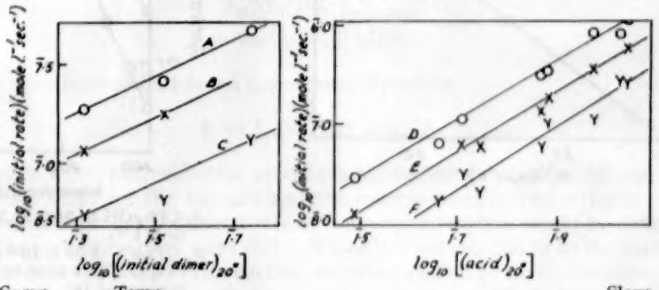
(ii) *Order in dimer and in acid.* The curves were analysed as for the forward runs, and the dependence of initial rate on initial monomer concentration (at constant acid concentration), and on acid concentration (at constant initial monomer concentration), is shown in Fig. 4 for different temperatures. It is seen that the order of reaction is 0·9 ± 0·2 in 1 : 1 : 3 : 3-tetraphenylbut-1-ene, and 3·0 ± 0·2 in acid. The scatter on these plots is more marked than for the forward reactions. These orders are again seen to be independent of temperature.

(iii) *Temperature-dependence.* In Fig. 3, curve *B*, is shown a typical result for the temperature-dependence of initial slope, obtained from the data of Fig. 4 as described for the forward run. The average value of the activation energy for this reverse reaction, E_r, obtained from plots of this type is 17·3 ± 1·5 kcal./mole.

Determination of Equilibrium Constant.—Since the forward and the reverse reaction are of the same order in acid, the value of the equilibrium constant, K, can be obtained from the equilibrium concentrations of monomer and dimer by using the expression $K = [\text{dimer}]_e/[\text{monomer}]_e^2$.

Thence the volume change, x, associated with the complete conversion of 1 mole of monomer into dimer has been found as follows. The value for K can be expressed in terms of x and the

FIGS. 4*a* and *b*. *Orders in dimer and acid.*



Curve	Temp.			Slope
A	54·7°	Acid concn. (mole l.$^{-1}$)	0·735	0·92
B	45·7	Acid concn. (mole l.$^{-1}$)	0·745	0·90
C	33·8	Acid concn. (mole l.$^{-1}$)	0·754	0·90
D	54·7	Dimer concn. (mole l.$^{-1}$)	0·3987	2·90
E	45·7	Dimer concn. (mole l.$^{-1}$)	0·4039	2·98
F	33·8	Dimer concn. (mole l.$^{-1}$)	0·4091	3·08

observed volume change of either the forward or the reverse reaction. By equating these alternative expressions values of x were obtained which were the same within ±1·5% for several pairs of forward and backward reactions. This establishes that true equilibrium is reached from both directions. Knowing the volume change for the complete conversion of monomer into dimer we have determined the equilibrium concentrations of these two olefins and thence the equilibrium constant, K, according to the above equation (see Table 1). K was reproducible within ±2·5% at each temperature. Further, the knowledge of the volume change for complete conversion of monomer into dimer together with the information obtained about the order in olefin and acid of the forward and reverse reactions enables us to convert the values of the initial slopes of the reaction curves into rate constants. These values are given in Table 1 where k_f is the rate constant for the forward reaction and k_r that for the reverse reaction, calculated from the expressions :

$$\text{Initial rate of forward reaction} = k_f[\text{acid}]^{3\cdot1} \times [\text{initial monomer}]^2$$

$$\text{Initial rate of reverse reaction} = k_r[\text{acid}]^{3\cdot1} \times [\text{initial dimer}]$$

Since trichloroacetic acid exists completely in the dimer form in benzene (Bell and Arnold, *J.*, 1935, 1432), we have used the molecular weight of the acid dimer in evaluating the velocity constants.

Plotting the change of $\log_{10} K$ with $1/T$ (Fig. 5) gives a good straight line and the value of the exothermicity of reaction, Q, obtained from the slope of the line is 10·1 ± 0·5 kcal./mole.

Action of Trichloroacetic Acid as a Solvent.—The high order in trichloroacetic acid found in these experiments suggests that it is behaving in a dual capacity, as proton donor, and as solvent

for the ions so produced. To examine the ability of this acid to cause ionization, in circumstances where no proton addition to a double bond can occur, it was added to benzene solutions of triphenylmethyl chloride and tri-*p*-tolylmethyl chloride. These solutions were so dilute that in the absence of trichloroacetic acid they were colourless. On addition of a very small amount of the acid, the yellow colour characteristic of the triarylmethyl ion was produced. This was established by measuring the spectrum of the solution (cf. *e.g.*, Fig. 6).

FIG. 5. *Temperature-dependence of equilibrium constant.*

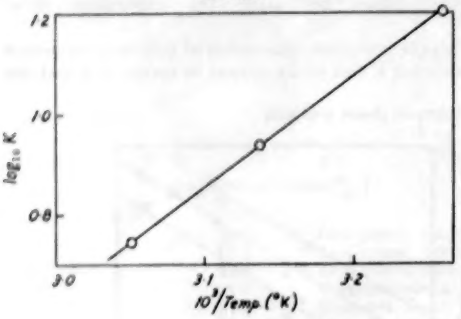
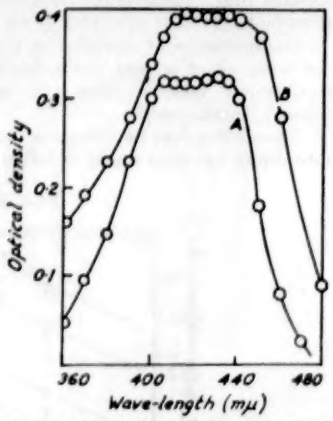


FIG. 6. *Spectrum of triphenylmethylcarbonium ion.*



A, $CPh_3{\cdot}OH$ in 98% H_2SO_4 ($8{\cdot}9 \times 10^{-6}$ mole $l.^{-1}$).
B, CPh_3Cl ($5{\cdot}59 \times 10^{-3}$ mole $l.^{-1}$), and $CCl_3{\cdot}CO_2H$ ($1{\cdot}32 \times 10^{-1}$ mole $l.^{-1}$) in benzene at 18°.

Discussion

Reaction Mechanism.—The mechanism must be in accord with the following experimental results. (*a*) The dimerization reaction of 1 : 1-diphenylethylene to 1 : 1 : 3 : 3-tetraphenylbut-1-ene is of second order in monomer, and of third order in trichloroacetic acid. (*b*) The formation of 1 : 1-diphenylethylene from 1 : 1 : 3 : 3-tetraphenylbut-1-ene is of first order in dimer and of third order in trichloroacetic acid. We interpret these results according to the annexed scheme.

$$3AH + CH_2{:}CPh_2 \underset{b}{\overset{a}{\rightleftharpoons}} (Me{\cdot}CPh_2{}^+A^-)_{solv.\ 2AH}$$

$$(Me{\cdot}CPh_2{}^+A^-)_{solv.\ 2AH} + CH_2{:}CPh_2 \underset{b}{\overset{a}{\rightleftharpoons}} (Me{\cdot}CPh_2{\cdot}CH_2{\cdot}CPh_2{}^+A^-)_{solv.\ 2AH}$$

$$(Me{\cdot}CPh_2{\cdot}CH_2{\cdot}CPh_2{}^+A^-)_{solv.\ 2AH} \underset{b}{\overset{a}{\rightleftharpoons}} Me{\cdot}CPh_2{\cdot}CH{:}CPh_2 + 3AH$$

where AH is trichloroacetic acid, and the solvation of the ion pairs includes 2AH molecules.

We may write this more simply as:

$$3AH + M \underset{b}{\overset{a}{\rightleftharpoons}} (HM^+A^-)_{solv.\ 2AH} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$(HM^+A^-)_{solv.\ 2AH} + M \underset{b}{\overset{a}{\rightleftharpoons}} (HD^+A^-)_{solv.\ 2AH} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$(HD^+A^-)_{solv.\ 2AH} \underset{b}{\overset{a}{\rightleftharpoons}} D + 3AH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where M stands for monomer, and D for dimer. In this scheme three molecules of acid are involved in the addition of a proton to the double bond; one molecule acts as a proton donor, and the other two take part in solvating the resulting ion pair. These ions must exist as ion pairs to give the observed kinetic results.

If the rate-controlling step for the forward reaction were reaction (2*a*) then the initial rate of dimerization, as given by the initial slope of the volume decrease–time curve, would be:

$$k_{2a}[(HM^+A^-)_{solv.\ 2AH}][M]$$
$$= k_{2a}(k_{1a}/k_{1b})[AH]^3[M]^2$$

This is of the same form as that found experimentally, where

$$k_f = k_{2a}(k_{1a}/k_{1b}) = k_{2a} \cdot K_1$$

Similarly, if the rate-controlling step for the reverse reaction were reaction (2*b*), then the initial rate of the reverse reaction, as given by the initial slope of the volume increase–time curve, would be:

$$k_{2b}[(HD^+A^-)_{solv.\ 2AH}]$$
$$= k_{2b}(k_{3b}/k_{3a})[AH]^3[D]$$

This is of the same form as that found experimentally where

$$k_r = k_{2b}(k_{3b}/k_{3a}) = k_{2b}/K_3$$

Thus, our results are explained by the above mechanism with reactions (2*a*) and (2*b*) as the rate-determining steps for the forward and the reverse reaction respectively. The same order in acid and dimer for the initial rate of the reverse reaction would be obtained if the slow step in the reverse reaction were (3*b*). We do not believe this to be the case, however, as both the forward and the reverse reaction are accompanied by an instantaneous development of colour which we attribute to the establishment of equilibria (1) and (3), since the ion formed by adding a proton to 1 : 1-diphenylethylene is coloured [A. G. Evans and Hamann, *Proc. Roy. Dublin Soc.*, 1950, **25** (N.S.), 139; A. G. Evans, *loc. cit.*].

Velocity Constants and Equilibrium Constant.—From the dependence of the initial rates of the forward and th reverse reaction on the olefin and acid concentrations, we have established that the order of reaction in the forward direction is 2 in monomer and 3 in acid, and in the reverse direction is 1 in dimer and 3 in acid. From the dependence of the equilibrium concentrations of monomer and dimer on the total amount of olefin present, we have established that the ratio of the orders of reaction in the forward and the reverse direction is 2 : 1 for monomer : dimer, and that both reactions are of the same order in acid. In this respect, then, both the kinetic analysis of the reaction rates and the determination of the equilibrium conditions of the system are in agreement.

Temp.	$10^7 k_f$ * (mole$^{-4\cdot1}$ l.$^{4\cdot1}$ sec.$^{-1}$) (initial slope)	$10^7 k_r$ * (mole$^{-3\cdot1}$ l.$^{3\cdot1}$ sec.$^{-1}$) (initial slope)	$10^7 k_r$ * (mole$^{-3\cdot1}$ l.$^{3\cdot1}$ sec.$^{-1}$) $= k_f/K$	k_f/k_r (mole^{-1} l.)	K (mole^{-1} l.)
33·8°	18·2	4·8	1·15	3·8	15·85
45·7	32·5	13·0	3·78	2·5	8·59
54·7	45·0	27·1	8·04	1·7	5·60

* k_f and k_r are evaluated in terms of the number of moles per l. of dimer appearing and disappearing respectively per sec.

We should expect the ratio of the velocity constants, k_f/k_r, to equal the value of K determined from the equilibrium conditions of the system. It is seen from the Table that the k_f/k_r ratios are lower than the corresponding K values. We believe K to be the more accurate, since the amounts of dimer present at equilibrium, determined (*a*) by weighing, and (*b*) by volume change, agree, as mentioned above, to within 4%. As regards the k_f and k_r values obtained from the initial slopes of the forward and reverse reactions respectively, and given in the Table, we believe the former to be the more accurate. The

volume changes associated with the reverse reactions are much smaller than those for the forward reactions, making k_r less reliable than k_f; indeed Figs. 4*a* and 2*a* show that the reproducibility of k_r is much less than that of k_f. Further, we have found that, unless rigorous precautions are taken in purifying the dimer, large initial slopes may be obtained for the reverse reactions although the m. p. of the dimer used is correct. This suggests that, even in the purest samples of dimer we have made, some trace impurity may still remain, which accelerates both the reverse and the forward reactions and does not affect the final equilibrium position. Although the monomer has been purified in several different ways, we have never found any such variation in the values for the initial slope of the forward reaction. We believe, therefore, that the best values of k_r are obtained from the forward reactions, that is, from the ratio k_f/K. The values obtained in this way are given in the Table.

According to our mechanism the equilibrium constant, K, is related to the individual rate constants as follows:

$$K = \frac{k_f}{k_r} = \frac{k_{1a}}{k_{1b}} \cdot \frac{k_{2a}}{k_{2b}} \cdot \frac{k_{3a}}{k_{3b}} = K_1K_2K_3$$

Activation Energies and Heats of Reactions.—The activation energies for the forward and the reverse reaction, obtained from the temperature dependence of the initial slopes and the exothermicity of the dimerisation reaction Q are:

$$E_f = 9{\cdot}1 \text{ kcal. mole}^{-1}. \quad E_r = 17{\cdot}3 \text{ kcal. mole}^{-1}.$$
$$E_r - E_f = 8{\cdot}2 \text{ kcal. mole}^{-1}. \quad Q = 10{\cdot}1 \text{ kcal. mole}^{-1}.$$

The activation energy for the forward reaction, E_f, will be the sum of the endothermicity of reaction (1*a*) and the activation energy of reaction (2*a*). The activation energy for the reverse reaction, E_r, will be the sum of the endothermicity of reaction (3*b*) and the activation energy of reaction (2*b*). The difference of these ($E_r - E_f$), 8·2 kcal./mole, is in fair agreement with the value 10·1 kcal./mole for the exothermicity of the dimerization reaction, Q, obtained from our equilibrium measurements. From the above discussion regarding the accuracy of k_r, we believe that a better value for E_r is given by $(E_f + Q) =$ 19·2 kcal./mole. Although the activation energies are small, the forward and the reverse reactions are extremely slow. This will be so because the transition-state complex involves not only two olefin molecules in special orientation, but also three trichloroacetic acid molecules (in addition to any benzene solvating the complex), and thus the entropy of activation, and hence the temperature-independent factor, will be very small indeed.

It has been shown in earlier work on the polymerization of *iso*butene and methyl methacrylate that the bulky side groups reduce the heat of polymerization below that expected theoretically (A. G. Evans and Tyrrall, *J. Polymer Sci.*, 1947, **2**, 387). In the reaction now studied, the bulky phenyl groups prevent the reaction from proceeding beyond the dimer, and we may thus expect that the exothermicity of reaction, 10·1 kcal./mole, is lower than it otherwise would be because of steric compressions which are present in the dimer but not in the monomer. The extent of this steric hindrance was demonstrated when a model of the dimer was made. Using Courtauld atomic models, which allow some distortion of bonds, it was impossible to make the dimer unless more flexible links were used: even then great difficulty was experienced.

Solvation of Ions.—Our postulate that the trichloroacetic acid acts as a solvent for the ion pairs is justifiable. Acetic acid can solvate ion pairs of the type R^+Cl^- where R is a triarylmethyl group, and this property is more marked than would be expected from the value of the dielectric constant of acetic acid (A. G. Evans, Price, and Thomas, *Trans. Faraday Soc.*, in the press). This ability to act as a solvent for ionization has been demonstrated for trichloroacetic acid (cf. above) since this acid produced ionization of triarylmethyl chlorides in benzene. Further confirmation has been obtained from recent experiments on the dimerization of 1 : 1-diphenylethylene, catalysed by trichloroacetic acid, in nitroethane, which is more polar than benzene. Here we find the forward reaction to be of second order in monomer and of order 2·4 in acid, and the reverse reaction to be of first

order in dimer and of order 2·4 in acid. The smaller order in acid is to be expected in this more polar solvent, since nitroethane is quite an efficient solvent for the ionization of triarylmethyl halides (Bentley, A. G. Evans, and Halpern, *Trans. Faraday Soc.*, 1951, **47**, 711; Bentley and A. G. Evans, *J.*, 1952, 3468), and will thus play a more important part than will benzene in the solvation of the ion pairs formed in the reaction of 1 : 1-diphenylethylene.

The fact that the catalyst in these reactions not only acts as a proton donor to the olefin, but also takes part in solvating the ions so formed, is of great significance. Thus, in general, quite an appreciable part of the efficiency of a cationic catalyst, especially in solvents of low ionizing power, may be determined by its contribution to the solvation of the ionic intermediates of the reaction.

UNIVERSITY COLLEGE, CARDIFF. [*Received, January 12th*, 1955.]

Ester and Lactone Linkages in Acidic Polysaccharides. Part II. Lactones of* D-*Glucosaminic Acid.*

By D. B. HOPE and P. W. KENT.

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Methylation and hydrolysis of ethyl *N*-benzoyl-4 : 6-*O*-benzylidene-D-glucosaminate leads to the crystalline 2-benzamido-2-deoxy-3 : 5-di-*O*-methyl-D-glucono-1 : 4-lactone. Evidence has been found for the lactonisation of anionic salts ($^-NH_3^+$) of D-glucosaminic acid and of its *N*-acetyl, -toluene-*p*-sulphonyl, and -2 : 4-dinitrophenyl derivatives. *N*-Benzoyl-D-glucosaminic acid has been characterised as a 1 : 5-lactone.

IN Part I* the susceptibility of certain acidic polysaccharides to lactonisation was correlated with the positions of the glycosidic linkages. We have now investigated the influence, on the course of lactonisation, of a 2 amino-group, as exemplified by D-glucosaminic acid (2-amino-2-deoxy-D-gluconic acid) and its derivatives.

In general, attempts to isolate D-gluconic acid from solution have resulted in the formation of a 1 : 4- or 1 : 5-lactone, whereas by the same processes D-glucosaminic acid is invariably obtained as the free acid. The results of Fischer and Leuchs (*Ber.*, 1903, **36**, 24) suggest however that conditions exist in which derivatives of glucosaminic acid lactonise, as in the reduction of D-glucosaminic acid to D-glucosamine. Lactones of *N*-acetyl-D-galactosaminic acid (Karrer and Meyer, *Helv. Chim. Acta*, 1937, **20**, 407) and *N*-methyl-L-glucosaminic acid (Wolfrom, Thompson, and Hooper, *Science*, 1946, **104**, 276) have also been described although their ring form has not been characterised : in these instances, the amino-group was substituted. In order to study the unambiguous behaviour of a 1 : 4-lactone, 2-benzamido-2-deoxy-3 : 5-di-*O*-methyl-D-glucono-1 : 4-lactone was synthesised by the following reactions. D-Glucosaminic acid with benzaldehyde in acidic conditions afforded a compound (m. p. 129°) having the analytical composition of ethyl 4 : 6-*O*-benzylidene-D-glucosaminate hydrochloride. The compound failed to form a hydroxamic acid, as other α-amino-esters do, and when recrystallised from pryidine–methanol gave 4 : 6-*O*-benzylidene-D-glucosaminic acid. It was therefore concluded that the compound was 4 : 6-*O*-benzylidene-D-glucosaminic acid hydrochloride with one molecule of ethanol of crystallisation. The existence of this compound may explain the divergent melting points (200°, Levene, *J. Biol. Chem.*, 1922, **53**, 449; 167—168°, Levene and La Forge, *ibid.*, 1915, **21**, 345; 126°, Levene, "Hexosamines and Mucoproteins," London, Longmans, 1926) reported for ethyl 4 : 6-*O*-benzylidene-D-glucosaminate.

The true ester hydrochloride, obtained from the above benzylidene compound by reaction with hot ethanolic hydrogen chloride, was converted into crystalline *N*-benzyloxycarbonyl and *N*-benzoyl esters. Methylation of the latter by Purdie's reagents resulted in a

* Part I, *J.*, 1953, 79.

liquid di-*O*-methyl derivative which after mild hydrolysis gave crystalline 2-benzamido-2-deoxy-3 : 5-di-*O*-methyl-D-glucono-1 : 4-lactone. The 1 : 4-lactone structure is supported by (i) the elementary composition, (ii) the neutrality of the compound and its reaction with one mol. of alkali, (iii) the formation of a hydroxamic acid under the same conditions as D-glucono-1 : 4-lactone gives one, and (iv) the resemblance of the rate of mutarotation ($[\alpha]_D^{20}$ $+77° \rightarrow +70°$ in 10 days) to that of 1 : 4-lactones.

Benzoylation of D-glucosaminic acid yielded a crystalline derivative having the properties of 2-benzamido-2-deoxy-D-glucono-1 : 5-lactone. This substance readily formed a hydroxamic acid and, in contrast to the 1 : 4-lactone, mutarotated rapidly ($[\alpha]_D^{21}$ $+118° \rightarrow 42°$ in 36 hr.) in common with other 1 : 5-lactones. It reacted readily with hydrazine and phenylhydrazine, giving hydrazide and phenylhydrazide.

Acetylation of D-glucosaminic acid with keten gave a non-crystalline product which nevertheless exhibited typical relations of a lactone. The *N*-2 : 4-dinitrophenyl derivative of the derived acid crystallised from aqueous solution as a lactone, as also did the *N*-toluene-*p*-sulphonyl derivative.

D-Glucosaminic acid, on the other hand, failed to form a hydroxamic acid even after being heated in the dry state at temperatures between 25° and 200° for 0·5—3 hr. The acid, heated or otherwise, had zero optical rotation in aqueous solution when examined in sodium-D light or at 5461 Å. In dilute hydrochloric acid (2·5% w/v), D-glucosaminic acid exhibited mutarotation ($[\alpha]_D^{21}$ $-16·5° \rightarrow -14°$ in 48 hr.).

It is consistent with these results to ascribe the failure of D-glucosaminic acid to lactonise to zwitterion formation (Sidgwick, "Organic Chemistry of Nitrogen," Oxford, 1937). This is known to be an exothermic reaction: the reaction $NH_2 \cdot CH_2 \cdot CO_2H \longrightarrow {}^+NH_3 \cdot CH_2 \cdot CO_2^-$ has ΔH $-11·5 \pm 1$ kcal./mole. It appears likely therefore that similar ionization stabilises D-glucosaminic acid. In acidic solution or other conditions for *N*-substituted glucosaminic acids where zwitterion formation is impossible, lactonisation appears to take the course usual for hexonic acids.

Experimental.

D-Glucosaminic Acid.—D-Glucosamine hydrochloride (10 g.) in water (100 ml.), mixed with freshly precipitated yellow mercuric oxide (30 g.) suspended in water (400 ml.), was heated with stirring at 95—100° for 25 min. The filtered solution was treated with hydrogen sulphide and, after separation of the precipitate, was concentrated at 50° under reduced pressure until crystallisation was observed. An equal volume of hot methanol was added. The product (6·7 g.), recrystallised from aqueous methanol, decomposed at 250° and had $[\alpha]_D^{22}$ 0° ± 2° in H_2O (*c* 0·83), $[\alpha]_D^{21}$ $-16·5° \longrightarrow -14°$ in 2·5% HCl (*c* 1·64) (Found: N, 7·1. Calc. for $C_6H_{13}O_5N$: N, 7·2%).

4 : 6-O-*Benzylidene*-D-*glucosaminic Acid Hydrochloride*.—The preceding acid (2 g.) in dry ethanol (15 ml.) and freshly distilled benzaldehyde (3 ml.) was saturated with dry hydrogen chloride at room temperature. The mixture which rapidly solidified was washed with ether (100 ml.), and the residue recrystallised from dry ethanol. The solvated **4 : 6-O-*benzylidene*-D-*glucosaminic acid hydrochloride*** (2·9 g.) had m. p. 129°, $[\alpha]_D^{26}$ $-54·4°$ (*c* 0·65 in MeOH), $[\alpha]_D^{26}$ $-30·2°$ (*c* 0·86 in H_2O) (Found: C, 49·4; H, 6·3; N, 4·0; OEt, 13·3. $C_{15}H_{24}O_7NCl$ requires C, 49·1; H, 6·55; N, 3·8; OEt, 13·0%). When recrystallised from methanol containing 5% of pyridine (or an equivalent amount of ammonia or hydroxylamine) this yielded **4 : 6-*O*-**benzylidene-D-glucosaminic acid (Levene, *J. Biol. Chem.*, 1922, **53**, 449), m. p. 214—220 (decomp.) (Found: C, 55·0; H, 5·9; N, 4·7. Calc. for $C_{13}H_{17}O_6N$: C, 55·1; H, 6·05; N, 4·9%).

Ethyl **4 : 6-O-*Benzylidene*-D-*glucosaminate Hydrochloride*.**—The above benzylidene derivative (3 g.) was dissolved in ethanol (10 ml.), and the solution saturated with dry hydrogen chloride. After 3 hr. ether (1 vol.) was added and the resulting ester (2·6 g.), recrystallised from dry ethanol, had m. p. 168°, $[\alpha]_D^{23}$ $-31·7°$ (*c* 0·98 in H_2O) (Found: C, 51·9; H, 6·3; N, 4·1; Cl, 10·5. Calc. for $C_{15}H_{22}O_6NCl$: C, 51·8; H, 6·3; N, 4·0; Cl, 10·2%).

Ethyl **N-*Benzoyl*-4 : 6-O-*benzylidene*-D-*glucosaminate*.**—The foregoing ester salt (3 g.) was dissolved at 0° in water (20 ml.) containing sodium hydrogen carbonate (1·8 g.), and benzoyl chloride (1·2 ml.) was added in 0·1-ml. portions, with continuous shaking, during 30 min. The resulting solid was recrystallised from ethanol, and the **N-*benzoyl ester*** (3·5 g.) had m. p. 167—168°, $[\alpha]_D^{22}$ $-81·3°$ (*c* 1·92 in $CHCl_3$) (Found: C, 63·7; H, 6·2; N, 3·4. $C_{22}H_{25}O_7N$ requires C, 63·6; H, 6·0; N, 3·4%).

Ethyl 4 : 6-O-*Benzylidene*-N-*benzyloxycarbonyl*-D-*glucosaminate*.—The ester salt (0·5 g.) was treated with benzoyl chloroformate (0·8 g.), water (5 ml.), and sodium hydrogen carbonate (0·3 g.). The resulting *product* (0·62 g.), recrystallised from ethanol, had m. p. 141—142°, $[\alpha]_D^{22}$ −56·4° (*c* 1·12 in $CHCl_3$) (Found: C, 62·0; H, 6·3; N, 3·1. $C_{33}H_{37}O_8N$ requires C, 62·0; H, 6·1; N, 3·1%).

2-*Benzamido*-2-*deoxy*-3 : 5-*di*-O-*methyl*-D-*glucono*-1 : 4-*lactone*.—Ethyl *N*-benzoyl-4 : 6-*O*-benzylidene-D-glucosaminate (3 g.) was boiled with dry acetone (5 ml.), methyl iodide (10 ml.), and dry silver oxide (10 g.) for 4 hr. Fresh methyl iodide (5 ml.) and silver oxide (5 g.) were added and the mixture heated for a similar period. The product obtained on evaporation of the filtered solution was remethylated in the same way. The *di*-O-*methyl* derivative, n_D^{20} 1·5480, failed to crystallise (Found: OEt, 9·7; OMe, 13·5. $C_{24}H_{29}O_7N$ requires OEt, 10·2; OMe 13·8%).

The di-*O*-methyl compound (0·5 g.) was heated at 100° for 24 hr. with acetic acid (60% v/v; 10 ml.) and then concentrated under reduced pressure at 80°. The product was made alkaline with N-sodium hydroxide and set aside at room temperature for 3 hr. The solution, neutralised (phenolphthalein) with sulphuric acid, was concentrated under reduced pressure until an oil separated, which was caused to redissolve by addition of ethanol. When cooled to 0°, the *di*-O-*methyl*-1 : 4-*lactone* (0·08 g.) separated and had m. p. 186°, $[\alpha]_D^{20}$ +76·9° → +70° in 10 days (*c* 1 in 50% aqueous ethanol) (Found: C, 57·9; H, 6·7; N, 4·2. $C_{15}H_{19}O_6N$ requires C, 58·25; H, 6·15; N, 4·5%).

2-*Benzamido*-2-*deoxy*-D-*gluconohydrazide*.—The lactone (0·05 g.) was heated with 50% aqueous hydrazine hydrate (0·5 ml.) and the minimum amount of ethanol necessary for solution. On cooling, the *hydrazide* (0·046 g.) separated and after recrystallisation from ethanol had m. p. 196—197° (Found: C, 49·6; H, 5·9; N, 13·5. $C_{13}H_{19}O_6N_3$ requires C, 49·3; H, 6·1; N, 13·4%).

2-*Deoxy*-2-*toluene*-p-*sulphonamido*-D-*gluconolactone*.—D-Glucosaminic acid (2·06 g.), dissolved in N-sodium hydroxide (30 ml.), was shaken with toluene-*p*-sulphonyl chloride (2 g.) in ether (25 ml.). After 3 hr. the aqueous layer was neutralised with 5N-sulphuric acid (6 ml.), and the resulting solid recrystallised from ethanol. The *toluene*-p-*sulphonyl* derivative (2·8 g.) had m. p. 172—173°, $[\alpha]_D^{20}$ −24·7° (*c* 0·193 in 1 : 1 aq. EtOH) (Found: C, 42·4; H, 5·6; N, 3·6. $C_{13}H_{21}O_8NS$ requires C, 42·5; H, 5·7; N, 3·8%).

2-*Deoxy*-2-*toluene*-p-*sulphonamidogluconophenylhydrazide*.—The preceding derivative (0·06 g.) was heated for 30 min. on a water-bath with phenylhydrazine (0·04 g.) in methanol (3 ml.). The *phenylhydrazide* (0·052 g.) which separated from the cooled solution crystallised from ethanol and had m. p. 178—179° (Found: C, 50·6; H, 5·8; N, 9·8. $C_{19}H_{25}O_7N_3S$ requires C, 50·6; H, 6·7; N, 9·6%).

2-*Deoxy*-2 : 4-*dinitroanilino*-2-*gluconolactone*.—D-Glucosaminic acid (1 g.) was treated with N-sodium hydroxide (10 ml.) and 1-fluoro-2 : 4-dinitrobenzene and after 2 hr. the mixture was extracted with ether. The aqueous layer was acidified with 5N-hydrochloric acid (2·5 ml.). The resulting N-2 : 4-*dinitrophenyl* derivative (0·3 g.) after being thrice recrystallised from water had m. p. 193—194° (Found: C, 41·3; H, 3·6; N, 11·8. $C_{12}H_{12}O_9N_4$ requires C, 42·0; H, 3·8; N, 12·25%).

2-*Benzamido*-2-*deoxy*-D-*glucono*-1 : 5-*lactone*.—D-Glucosaminic acid (2 g.) in 0·8N-sodium hydroxide (25 ml.) was treated at 0° with benzoyl chloride (1·2 ml.). After acidification with 5N-hydrochloric acid and filtration a solid separated from the cooled solution. The *lactone* (0·6 g.), recrystallised from ethanol, had m. p. 192—193°, $[\alpha]_D^{21}$ +118° → +42° in 36 hr. (*c* 0·57 in H_2O) (Found: C, 55·7; H, 5·6; N, 4·5. $C_{13}H_{15}O_6N$ requires C, 55·5; H, 5·3; N, 5·0%).

An aqueous solution (10 ml.) of the lactone (57·1 mg.) exhibited the following rotations at 21°: 0·69° (0 hr.), 0·51° (6 hr.), 0·40° (12 hr.), 0·33° (18 hr.), 0·28° (24 hr.), 0·24° (const., 36 hr.).

2-*Benzamido*-2-*deoxy*-N-*phenyl*-D-*gluconohydrazide*.—The preceding lactone (0·05 g.) with phenylhydrazine (0·03 g.) in hot ethanol (4 ml.) afforded after 30 min. a crystalline *phenylhydrazide* (0·052 g.) which, after recrystallisation from aqueous methanol, had m. p. 200—201° (Found: C, 58·3; H, 5·8; N, 10·8. $C_{19}H_{23}O_6N_3$ requires C, 58·6; H, 5·9; N, 10·8%).

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DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF OXFORD. [*Received, January 17th*, 1955.]

Purines, Pyrimidines, and Glyoxalines. Part I. New Syntheses of Glyoxalines and Pyrimidines.

By G. Shaw.

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Diacylamines R·CH_2·CO·NH·COR′ have been prepared; on nitrosation and hydrogenation they gave amines NH_2·CHR·CO·NH·COR′ which cyclised spontaneously or in dilute alkali to dihydroglyoxalines (IV). Reaction of *N*-acyl-*N*-cyanoacetylamines with ethyl orthoformate and acetic anhydride gave ethoxymethylene derivatives which with dilute aqueous ammonia yielded pyrimidines (VI), and with aniline and phenylhydrazine aminomethylene derivatives (VII); two of these cyclised to pyrimidines (VI) when heated. Reaction of cyanoacetic acid, acetic anhydride, ethyl orthoformate, and amides gave the acylamidomethylene derivatives (IX), whose structures were confirmed by independent syntheses, and a reaction mechanism for their formation is discussed.

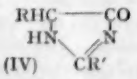
The formation of pyrimidines by cyclisation, under mild and possibly physiological conditions, of certain β-aminoacylamines, has been recorded by Shaw and Sugowdz (*J.*, 1954, 665). The present investigation had as its objects (*a*) the preparation of α-aminoacylamines (III) and an examination of their cyclisation to dihydroglyoxalines (IV) and (*b*) an investigation of simpler and more general methods for the preparation of β-aminoacylamines and thence of pyrimidines. A note (Shaw, *Chem. and Ind.*, 1954, 546) on some of the present work has been published.

The reputed preparation of diglycylamine $(NH_2·CH_2·CO)_2NH$ by reaction of bischloroacetylamine with ammonia (Bergell, *Z. physiol. Chem.*, 1907, **51**, 209; Abderhalden and Riesz, *Fermentforsch.*, 1930, **12**, 180) has been shown to be incorrect and the product is now formulated as iminobisacetamide $(NH_2·CO·CH_2)_2NH$ (Backés, *Bull. Soc. chim.*, 1948, 1184). A similar reaction of *N*-chloroacetylbenzamide with ammonia (Aberhalden and Riesz, *loc. cit.*) failed to give the required amine; this reaction in our hands was also unsuccessful. It was considered, however, that the most useful intermediates for the preparation of the required α-aminoacylamines would be compounds of type (I) where R

R·CH_2·CO·NH·COR′ (I)

R·C(:N·OH)·CO·NH·COR′ (II)

R·CH(NH_2)·CO·NH·COR′ (III)



(IV)

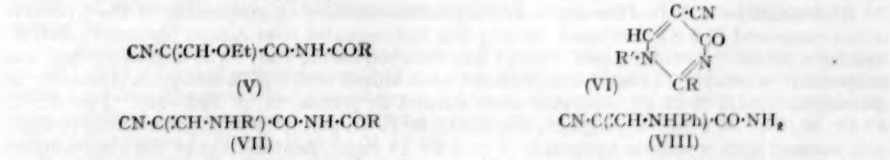
is an electrophilic group, in particular CN, CO_2R, or COR; introduction of an amino-group on to the active methylene group should then follow by standard methods. Compounds containing one such group (I; R = Ph·CO) have already been prepared (Shaw and Sugowdz, *loc. cit.*) by hydrogenation of a 5-acylamido-3-phenyl*iso*oxazole and hydrolysis of the amine so formed. Two of these amides (I; R = Ph·CO, R′ = Ph or Me) readily gave nitroso-compounds (II; R = Ph·CO, R′ = Ph and Me); the compound (II; R = Ph·CO, R′ = Ph) was easily hydrogenated to the amine (III; R = Ph·CO, R′ = Ph) which cyclised to the glyoxaline (IV; R = Ph·CO, R′ = Ph) in warm dilute aqueous sodium hydroxide.

Preparation of the amides (I; R = Ph·CO) was somewhat laborious, even after improvement, and attention was turned to the cyanoacetyl- and malonyl-amides (I; R = CN and CO·NH·COR′ respectively). Cyanoacetamide or malonamide with acid anhydrides alone (Hentschel, *Ber.*, 1890, **23**, 2395) or in the presence of hydrogen chloride (Polya and Tardrew, *J.*, 1948, 1081) or with acid halides (Titherley and Holden, *J.*, 1912, **101**, 1880) were unchanged or decomposed, possibly owing to dehydration to the unstable malononitrile. Reaction of cyanoacetyl or malonyl chloride with simple amides or of chloroacetylamides with metal cyanides also failed to give the desired compounds. Now cyanoacetylurethane (I; R = CN, R′ = OEt) and the malonylbisurethane $CH_2(CO·NH·CO_2Et)_2$ have been prepared by heating on a water-bath for a few hours a

mixture of cyanoacetic or malonic acid respectively with urethane and acetic anhydride (Conrad and Schulze, *Ber.*, **1909**, **42**, 734). Urethane is, of course, more readily acylated than simple aliphatic or aromatic amides; however, when it was replaced in the above reactions by acetamide or benzamide, the required diacylamides (I; R = CN, R′ = Me and Ph) and (I; R = CO·NH·COMe, R′ = Me; R = CO·NH·COPh, R′ = Ph) were readily obtained. Nitrosation of these compounds in water or acetic acid gave, almost quantitatively, the hydroxyimino-compounds (II). Hydrogenation of the malonyl derivative (II; R = CO·NH·COMe, R′ = Me) as a suspension in ethanol, with platinum or nickel catalysts, gave an alcohol-insoluble residue which was largely soluble in hydrochloric acid; attempts to separate this compound, presumably the base (III; R = CO·NH·COMe, R′ = Me), from the catalyst by crystallisation from water gave the dihydroglyoxaline (IV; R = CO·NH·COMe, R′ = Me) and alkaline hydrolysis of this gave the carbamylglyoxaline (IV; R = CO·NH_2, R′ = Me). Similar hydrogenation of the nitrosocyanoacetyl compound (II; R = CN, R′ = Me) in ethanol gave a soluble product from which the glyoxaline derivative (IV; R = CN, R′ = Me) alone could be isolated; the amino-nitrile (III; R = CN, R′ = Me) is, however, present in solution (unpublished work). Hydrogenation of the benzoyl-hydroxyimino-compounds (II; R = CN and CO·NH·COPh, R′ = Ph), however, gave the more stable amines (III) which readily gave the corresponding glyoxalines (IV; R = CN and CO·NH·COPh, R′ = Ph) in dilute aqueous sodium hydroxide.

The cyanoacetylamines (I; R = CN, R′ = Me, Ph, and OEt) with molar quantities of ethyl orthoformate and acetic anhydride under reflux rapidly gave the crystalline ethoxymethylene derivatives (V; R′ = Me, Ph, and OEt), but the malonylamines failed to react. The ethoxymethylene compound (V; R = OEt) rapidly dissolved in 1% aqueous ammonia at room temperature and acidification then gave an excellent yield of 5-cyanouracil (VI; R = OH, R′ = H or the keto-isomer) which was readily converted into uracil by hydrolysis and decarboxylation. Similar treatment with methylamine in place of ammonia gave 5-cyano-1-methyluracil (VI; R = OH, R′ = Me). The pyrimidines (VI; R = Me and Ph, R′ = H) were obtained similarly from the corresponding ethoxymethylene derivatives and ammonia. These are perhaps the simplest pyrimidine syntheses yet recorded and can be regarded as taking place under "physiological" conditions. The pyrimidine (VI; R = Me, R′ = H) is of particular interest since it was an intermediate in a synthesis of thiamine (Todd and Bergel, *J.*, **1937**, 364).

The compounds (V; R = Me, Ph, and OEt) with ethanolic solutions of aniline and phenylhydrazine at room temperature gave the linear aminomethylene derivatives (VII; R = Me, Ph and OEt, R′ = Ph and NHPh) smoothly and rapidly. Two of these, (VII; R = OEt, R′ = Ph and Ph·NH), when heated for a short time near the melting point, gave quantitively the pyrimidines (VI; R = OH, R′ = Ph and Ph·NH). A single attempt to cyclise the compound (VII; R = Me, R′ = Ph) with aqueous sodium hydroxide resulted in hydrolysis to the amide (VIII).



It was considered possible that the ethoxymethylene compounds (V) might be obtained even more simply from cyanoacetic acid, ethyl orthoformate, an amide, and acetic anhydride. However, use of acetamide, benzamide, or urethane, gave different (isomeric) products, hydrolysed by alkali to ammonia, carbon dioxide, cyanoacetaldehyde, and, from the benzamide product, benzoic acid; the same products were formed by hydrolysis of the compounds (V; R = Me, Ph, and OEt). These isomers were singularly resistant to ammonia or aniline: *e.g.*, the isomer derived from benzamide failed to react with aniline in boiling ethanol but with ammonia it slowly gave benzamide. However, with aqueous methylamine each of the isomers gave the same substance $C_7H_{10}O_2N_2$ which

could only arise by replacement of R·CO·NH by Me·NH. These reactions established the presence of the grouping CN·C(:CH·)·CO·, so the isomers were geometrical isomers of the diacylamine (V) or the esters (IX), and the substance formed by reaction with methylamine was the amide (X) or the ester (XI).

$CN{\cdot}C(:CH{\cdot}NH{\cdot}COR){\cdot}CO_2Et$ (IX) $\quad$ $CN{\cdot}C(:CH{\cdot}OEt){\cdot}CO{\cdot}NHMe$ (X) $\quad$ $CN{\cdot}C(:CH{\cdot}NHMe){\cdot}CO_2Et$ (XI)

Models of the two forms of (V) showed that, in one, close approach of the NH group and the ethereal oxygen occurred, leading possibly to considerable internal hydrogen bonding; however, the formation of the monoacylamine (X) from such compounds seemed unlikely. The formation of the esters (IX) appears to be more complex but would be possible by the reaction sequence: $CN{\cdot}CH_2{\cdot}CO_2H \longrightarrow CN{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}COMe \longrightarrow CN{\cdot}C(:CH{\cdot}OEt){\cdot}CO{\cdot}O{\cdot}COMe \longrightarrow CN{\cdot}C(:CH{\cdot}O{\cdot}COMe){\cdot}CO_2Et \longrightarrow$ (IX). Several analogues of (IX), notably acetamidomethylenemalononitrile (Passalacqua, *Gazzetta*, 1913, **43**, II, 566) and ethyl acetamido(and benzamido)-methyleneacetoacetate (Claisen, *Annalen*, 1897, **297**, 31), have been prepared by heating the appropriate ethoxymethylene derivative with an amide.

The compounds (IX; R = Me, Ph, and OEt) were accordingly synthesised by heating at 140—150° equimolar quantities of ethyl α-cyano-α-ethoxyacrylate and the appropriate amide; they were identical with the above-mentioned "isomers"; similarly, the amino-ester (XI) was prepared from methylamine and the cyano-ester and was identical with the compound $C_7H_{10}O_2N_2$ mentioned previously.

Experimental

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

N-Acetyl-α-benzoylacetamide (Shaw and Sugowdz, *loc. cit.*).—5-Acetamido-3-phenyl*iso*oxazole (*idem*, *loc. cit.*) (5 g.) in ethanol (250 ml.) was hydrogenated over Adams platinum catalyst until 1 mol. of hydrogen had been absorbed (1 hr.); the solution was filtered and warmed for a few minutes with 5N-hydrochloric acid (10 ml.). The solution was neutralised with aqueous ammonia, then evaporated to a small volume, cooled, filtered, and acidified with hydrochloric acid; *N*-acetyl-α-benzoylacetamide (2 g.) separated and, recrystallised from aqueous ethanol, had m. p. and mixed m. p. 104°. *N*-Benzoyl-α-benzoylamide was similarly prepared from 5-benzamido-3-phenyl*iso*oxazole.

Nitrosation of Benzoylacetamides.—To a cold solution of *N*-acetyl-α-benzoylacetamide (1 g.) in acetic acid (5 ml.) was added, dropwise and with shaking, a solution of sodium nitrite (0·5 g.) in water (5 ml.); a crystalline precipitate rapidly appeared; *N-acetyl-α-benzoyl-α-hydroxyiminoacetamide monohydrate* (0·8 g.) separated from ethanol as needles, m. p. 150° (decomp.) (Found: C, 52·6; H, 4·8; N, 11·4. $C_{11}H_{10}O_4N_2,H_2O$ requires C, 52·4; H, 4·8; N, 11·1%). The *N-benzoyl* derivative was similarly obtained as needles (from ethanol), m. p. 164° (decomp.) (Found: C, 64·65; H, 4·0; N, 9·25. $C_{16}H_{12}O_4N_2$ requires C, 64·85; H, 4·1; N, 9·5%).

Hydrogenation of N : *α-Dibenzoyl-α-hydroxyiminoacetamide.*—A suspension of the hydroxyimino-compound (0·5 g.) in ethanol (25 ml.) was hydrogenated over Adams platinum catalyst; hydrogen (85 ml. Calc. for 2 mol., 76 ml.) was absorbed during 1 hr. The filtered solution was evaporated *in vacuo*. The residue crystallised when stirred with a little water. *α-Amino*-N : *α-dibenzoylacetamide* (0·35 g.) separated from ethanol as prisms, m. p. 240—242° (Found: C, 67·15; H, 4·6; N, 9·85. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). The amine (0·25 g.) was warmed with N-sodium hydroxide (5 ml.) for 10 min. Acidification of the clear solution precipitated *5-benzoyl-4 : 5-dihydro-4-oxo-2-phenylglyoxaline* (0·2 g.) which separated from ethanol as prisms, m. p. >300° (Found: C, 72·4; H, 4·8; N, 10·9. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·5; N, 10·6%).

NN'-Diacetylmalonamide.—Malonic acid (50 g.), acetamide (60 g.), and acetic anhydride (200 g.) were heated on a water-bath for 4 hr., giving a dark-brown fluorescent solution which was cooled and filtered from a small amount of dark material, and the filtrate added to carbon tetrachloride (1 l.). A dark oil was precipitated which soon crystallised. It was filtered off and recrystallised three times from ethanol (charcoal) to give *NN'-diacetylmalonamide* (22 g.) as colourless needles, m. p. 138° (Found: C, 45·45; H, 5·5; N, 14·8. $C_7H_{10}O_4N_2$ requires C, 45·15; H, 5·4; N, 15·05%).

NN'-Diacetyl-α-hydroxyiminomalonamide.—*NN'*-Diacetylmalonamide (5 g.) was dissolved in warm water (40 ml.) containing sodium nitrite (1·85 g.); the solution was cooled to 5—10° (the amide occasionally crystallises out but generally there is little difficulty in obtaining a supersaturated solution) and 2N-hydrochloric acid (15 ml.) added dropwise with shaking; the *hydroxyimino-derivative* (5·5 g.) separated rapidly and recrystallised from methanol–water as needles, m. p. 190° (decomp.) (Found: C, 36·4; H, 4·75; N, 18·2. $C_7H_9O_5N_3,H_2O$ requires C, 36·05; H, 4·75; N, 18·05%). The compound gave a yellow solution with aqueous ammonia and a solution in aqueous sodium hydroxide gave a deep blue colour with ferrous sulphate.

Hydrogenation of NN'-Diacetyl-α-hydroxyiminomalonamide.—A suspension of the finely ground imino-compound (1 g.) in ethanol (30 ml.) was hydrogenated over Adams platinum catalyst; hydrogen (205 ml. Calc. for 2 mols., 192 ml.) was absorbed during 1 hr.; a crystalline precipitate remained, soluble in aqueous sodium hydroxide and in hydrochloric acid. The base crystallised from an excess of water to give *5-N-acetylcarbamoyl-4 : 5-dihydro-2-methyl-4-oxoglyoxaline* (0·75 g.) as colourless diamond-shaped plates, m. p. >300° (decomp. from 250°, and some sublimation) (Found: C, 45·6; H, 4·75; N, 23·15. $C_7H_9O_3N_3$ requires C, 45·9; H, 4·95; N, 22·95%), soluble in dilute sodium hydroxide solution and insoluble in hydrochloric acid. Light absorption in 0·02% aqueous sodium carbonate: $\lambda_{max.}$ 2300 (infl.) (ε 4600) and 3140 Å (ε 16,700). The compound gave an orange-yellow dye with diazotised sulphanilic acid. A solution of the glyoxaline (0·5 g.) in N-sodium hydroxide (5 ml.) was boiled for 2 min.; the cooled solution was acidified to precipitate *5-carbamoyl-4 : 5-dihydro-2-methyl-4-oxoglyoxaline* (0·35 g.) which crystallised from water as diamond-shaped plates, m. p. >300° (decomp. from 280°) (Found: C, 42·85; H, 5·0; N, 29·85. $C_5H_7O_2N_3$ requires C, 42·55; H, 4·95; N, 29·8%).

N-Acetyl-α-cyanoacetamide.—Cyanoacetic acid (17 g.), acetamide (11·8 g.), and acetic anhydride (37 ml.) were heated on a water-bath for 3 hr. Cooling gave a crystalline precipitate; *N-acetyl-α-cyanoacetamide* (8 g.) separated from ethanol (charcoal) as colourless plates, m. p. 156° (Found: C, 47·5; H, 5·0; N, 22·35. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·8; N, 22·2%); evaporation of the acetic acid solution and crystallisation of the residue gave a further quantity (5 g.) of the amide. A solution of the amide (1·26 g.) in ethanol (10 ml.) containing aniline (0·93 g.) was boiled for ½ hr.; water was added to the cooled solution to precipitate cyanoacetanilide (0·45 g.), m. p. and mixed m. p. 198°.

N-Acetyl-α-cyano-α-hydroxyiminoacetamide.—A solution of *N*-acetyl-α-cyanoacetamide (2·52 g.) in warm water (50 ml.) containing sodium nitrite (1·4 g.) was cooled to 5—10° and to the supersaturated solution was added 2·5N-hydrochloric acid (8 ml.) dropwise with shaking and cooling. The *hydroxyimino-compound* (2·3 g.) separated rapidly, and recrystallised from ethanol–water (1 : 1) as nacreous plates, m. p. 207° (decomp.) (Found: C, 34·45; H, 4·05; N, 24·25. $C_5H_5O_3N_3,H_2O$ requires C, 34·7; H, 4·1; N, 24·25%); the compound gave colour reactions similar to those of the analogous malonyl compound.

Hydrogenation. A solution of the amide (1 g.) in ethanol (40 ml.) was reduced over platinum, hydrogen (265 ml. Calc. for 2 mols., 259 ml.) being absorbed during 5 hr. The filtered solution was evaporated to dryness *in vacuo* to give a pale yellow solid which was washed with ether; *5-cyano-1 : 5-dihydro-2-methyl-4-oxoglyoxaline* (0·7 g.) crystallised from methanol as colourless laths, m. p. >300° (decomp. from 180° and sublimation) (Found: C, 48·5; H, 4·1; N, 33·9. $C_5H_5ON_3$ requires C, 48·75; H, 4·1; N, 34·15%), and formed a yellow dye with diazotised sulphanilic acid. The glyoxaline darkened when kept at room temperature for several days.

α-Cyano-β-ethoxy-N-ethoxycarbonylacrylamide.—*N*-Cyanoacetylurethane (Conrad and Schulze, *loc. cit.*) (3·12 g.), ethyl orthoformate (2·96 g.), and acetic anhydride (5 ml.) were boiled under reflux for 1 hr.; the crystalline *product* separated on cooling, was washed with light petroleum, and crystallised from benzene as needles (3·2 g.), m. p. 120° (Found: C, 50·8; H, 5·55; N, 13·45. $C_9H_{12}O_4N_2$ requires C, 50·95; H, 5·7; N, 13·2%).

β-Anilino-α-cyano-N-ethoxycarbonylacrylamide.—To a solution of the foregoing amide (0·2 g.) in ethanol (5 ml.) were added 2 or 3 drops of aniline; the *anilino-compound* crystallised almost immediately and separated from ethanol as prisms (0·2 g.), m. p. 167—170° (decomp.; resolidified and then had m. p. 290°) (Found: C, 60·35; H, 5·05; N, 16·45. $C_{13}H_{13}O_3N_3$ requires C, 60·2; H, 5·05; N, 16·2%).

5-Cyano-1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylpyrimidine.—The anilino-amide (0·1 g.) was kept at 200° (bath) for 2—3 min. It melted, effervesced, and resolidified. The solid residual *dione* separated from ethanol as plates, m. p. 290° (Found: C, 61·8; H, 3·3; N, 19·7. $C_{11}H_7O_2N_3$ requires C, 61·95; H, 3·3; N, 19·7%). Light absorption in 0·04% aqueous sodium carbonate: $\lambda_{max.}$ 2320 (ε 9650) and 2815 Å (ε 9750).

α-Cyano-N-ethoxycarbonyl-β-phenylhydrazinoacrylamide.—A solution of the ethoxyacrylamide (1 g.) in ethanol (5 ml.) was treated with phenylhydrazine (0·5 g.), giving gradually a crystalline precipitate; the yellow solid was collected and washed with ether which removed the colour; the *phenylhydrazino-urethane* (0·65 g.) separated from ethanol or benzene as colourless plates, m. p. 128—129° (Found: C, 57·15; H, 5·1; N, 20·55. $C_{12}H_{14}O_2N_4$ requires C, 56·95; H, 5·15; N, 20·45%). The ethanolic solution with ether gave a further quantity of material (0·2 g.); addition of acid or alkali to the ethanolic solution gave a cherry-red colour.

1-Anilino-5-cyano-1:2:3:4-tetrahydro-2:4-dioxopyrimidine.—The phenylhydrazinourethane (0·5 g.), when heated at 140—150° (bath) for 5 min., melted and then crystallised; the *pyrimidine* (0·4 g.) separated from water (*ca.* 150 ml.) as colourless needles, m. p. 334° (decomp.) (Found: C, 57·9; H, 3·55; N, 24·6. $C_{11}H_8O_2N_4$ requires C, 57·9; H, 3·55; N, 24·55%). Light absorption in 0·04% aqueous sodium carbonate: $\lambda_{max.}$ 2380 (ε 7600) and 2600 Å (infl.) (ε 900).

5-Cyanouracil.—The ethoxyacrylamide (1 g.) was treated with 1% aqueous ammonia (10 ml.). It dissolved in a few minutes to form a pale yellow solution, whence acetic acid, after a short time, precipitated 5-cyanouracil (0·6 g.), diamond-shaped plates (from ethanol), m. p. 280° (decomp.) (Found: C, 43·8; H, 2·3; N, 30·75. Calc. for $C_5H_3O_2N_3$: C, 43·8; H, 2·2; N, 30·65%); light absorption in 0·02% aqueous sodium carbonate: $\lambda_{max.}$ 2330 (ε 10,400) and 2900 Å (ε 11,400); the compound gave a purple precipitate when boiled with bromine water, then treated with barium hydroxide solution; Johnson (*Amer. Chem. J.*, 1909, **42**, 513) gives m. p. 295° (decomp.). The compound was formed in similar yield when more concentrated ammonia was used.

The compound (0·5 g.) was boiled with 50% sulphuric acid (5 ml.) for 1 hr., then was cooled, diluted with water (10 ml.), and set aside. Uracil-5-carboxylic acid monohydrate (0·35 g.) crystallised and separated from water as prisms, m. p. 285° (decomp.) (Found: C, 34·9; H, 3·6; N, 16·2. Calc. for $C_5H_4O_4N_2,H_2O$: C, 34·5; H, 3·45; N, 16·1%); Ballard and Johnson (*J. Amer. Chem. Soc.*, 1942, **64**, 794) give, for the monhydrate, m. p. 268—270° (effervescence). The acid (0·5 g.) was kept at 280° (bath) for a few minutes; carbon dioxide was evolved (barium hydroxide solution) and the residue, uracil, separated from water as prisms (0·3 g.), m. p. and mixed m. p. 320° (decomp.) (Found: C, 42·7; H, 3·55; N, 24·85. Calc. for $C_4H_4O_2N_2$: C, 42·85; H, 3·6; N, 25·0%).

5-Cyano-1-methyluracil.—The ethoxyacrylamide (1 g.) dissolved readily in warm aqueous methylamine (5 ml.; 28%) to give a pale yellow solution; this was boiled to remove excess of methylamine, cooled, and acidified with acetic acid. The colourless precipitate of *5-cyano-1-methyluracil* (0·7 g.) crystallised from ethanol (*ca.* 50 ml.) as needles, m. p. 256° (Found: C, 47·85; H, 3·25; N, 27·95. $C_6H_5O_2N_3$ requires C, 47·7; H, 3·35; N, 27·8%). The same compound was formed in slightly better yield when dilute aqueous methylamine was used.

N-Acetyl-α-cyano-β-ethoxyacrylamide.—A solution of *N*-acetyl-α-cyanoacetamide (3·1 g.), ethyl orthoformate (3·6 g.), and acetic anhydride (5 g.) was boiled under reflux for 1 hr. The pale brown solution was evaporated to a small volume *in vacuo* and cooled. The crystalline precipitate of the *acrylamide* (2·8 g.) separated from benzene or benzene–light petroleum as needles, m. p. 109° (Found: C, 52·65; H, 5·7; N, 15·5. $C_8H_{10}O_3N_2$ requires C, 52·75; H, 5·55; N, 15·4%).

The amide (0·5 g.) was boiled with N-sodium hydroxide (10 ml.) for 10 min.; a clear solution was soon obtained and ammonia was liberated. The solution was acidified with hydrochloric acid, carbon dioxide being evolved (barium hydroxide solution), then treated with 2:4-dinitrophenylhydrazine in 2N-hydrochloric acid to give a yellow precipitate of cyanoacetaldehyde 2:4-dinitrophenylhydrazone, needles (from ethanol), m. p. 170—171° (Found: C, 43·1; H, 2·75; N, 28·45. Calc. for $C_9H_7O_4N_5$: C, 43·4; H, 2·85; N, 28·1%).

N-Acetyl-β-anilino-α-cyanoacrylamide.—To a solution of the foregoing amide (1 g.) in ethanol (10 ml.) was added aniline (1 ml.); after a few seconds crystals of the *anilino-compound* separated; this crystallised from methanol as needles (1 g.), m. p. 202—204° (decomp.) (Found: C, 62·65; H, 4·75; N, 18·4. $C_{12}H_{11}O_2N_3$ requires C, 62·85; H, 4·85; N, 18·3%). A mixture of the amide (0·6 g.), ethanol (5 ml.), and 2N-sodium hydroxide (2 ml.) was boiled for 5 min.; the clear solution so obtained was diluted with water (5 ml.), and acidified with acetic acid to give a crystalline precipitate of *β-anilino-α-cyanoacrylamide* (0·3 g.), needles (from ethanol–water), m. p. 209—210° (Found: C, 63·65; H, 4·85; N, 22·35. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·85; N, 22·45%).

N-Acetyl-α-cyano-β-phenylhydrazinoacrylamide.—A solution of *N*-acetyl-α-cyano-5-ethoxyacrylamide (0·18 g.) in methanol (2 ml.), when treated with phenylhydrazine (0·11 g.), deposited crystals after a few minutes; the filtrate gave cherry-red colours with acid or alkali. The

β-*phenylhydrazino-compound* (0·1 g.) separated from methanol as needles, m. p. 212° (decomp.) (Found: C, 58·9; H, 4·9; N, 23·0. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·95; N, 22·95%).

Reaction of N-Acetyl-α-cyano-β-ethoxyacrylamide with Ammonia.—The ethoxy-amide (0·2 g.) was treated with 1% ammonia solution (5 ml.); the amide soon dissolved and the clear yellow solution was acidified with acetic acid and set aside. *5-Cyano-1:4-dihydro-2-methyl-4-oxopyrimidine* (0·1 g.) separated from ethanol–water as needles, m. p. 235° (decomp.) (Found: C, 53·3; H, 3·4; N, 31·1. Calc. for $C_6H_5ON_3$: C, 53·35; H, 3·7; N, 31·1%). Light absorption in 0·02% aqueous sodium carbonate: $\lambda_{max.}$ 2340 (ε 7700) and 2920 Å (ε 5900). Todd and Bergel (*loc. cit.*) give m. p. 233—235°.

N-(Cyanoacetyl)benzamide.—Cyanoacetic acid (14·8 g.), benzamide (21 g.), and acetic anhydride (23 ml.) were heated on a water-bath for 1½ hr. A brown solution was obtained which when cooled gave a crystalline precipitate which was filtered off and washed with ether; *N-(cyanoacetyl)benzamide* (7 g.) separated from ethanol (charcoal) as needles, m. p. 184° (Found: C, 63·6; H, 4·15; N, 14·75. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

N-Benzoyl-α-cyano-α-hydroxyiminoacetamide.—*N*-(Cyanoacetyl)benzamide (5 g.) was dissolved in warm acetic acid (100 ml.); the solution was cooled (the amide may crystallise but generally remains in solution) and to it was added, rapidly with shaking and cooling, a solution of sodium nitrite (1·8 g.) in water (5 ml.); a crystalline solid rapidly precipitated and was filtered off and washed with ether. The *hydroxyimino-compound* (3·9 g.) separated from ethanol as prisms, m. p. 205° (decomp.) (Found: C, 55·5; H, 3·2; N, 19·55. $C_{10}H_7O_3N_3$ requires C, 55·3; H, 3·25; N, 19·35%); a further quantity (0·9 g.) separated from the mother-liquors overnight.

Hydrogenation. A suspension of the foregoing amide (1 g.) in ethanol was hydrogenated over Adams platinum catalyst; hydrogen (201 ml. Calc. for 2 mols., 207 ml.) was absorbed during 4 hr. The solution was evaporated to dryness *in vacuo* and the solid *α-amino-N-benzoyl-α-cyanoacetamide* (0·6 g.) crystallised from ethanol as hexagonal prisms, m. p. >300° (decomp. from *ca.* 220°) (Found: C, 58·95; H, 4·3; N, 20·9. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·45; N, 20·7%). The amine (0·25 g.) was dissolved in N-sodium hydroxide (5 ml.) and kept at room temperature for 30 min.; the solution was acidified and the precipitate collected; *5-cyano-4:5-dihydro-4-oxo-2-phenylglyoxaline* (0·1 g.) separated from water as needles, m. p. >300° (Found: C, 64·65; H, 3·8; N, 22·9. $C_{10}H_7ON_3$ requires C, 64·85; H, 3·8; N, 22·7%).

NN'-Dibenzoylmalonamide.—Malonic acid (10 g.), benzamide (24 g.), and acetic anhydride (40 ml.) were heated on a water-bath for 3 hr. On cooling, a crystalline precipitate was obtained; this was filtered off and washed with ethanol and ether; *NN'-dibenzoylmalonamide* (14 g.) finally crystallised from ethanol as needles, m. p. 179—181° (Found: C, 65·65; H, 4·5; N, 9·05. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·55; N, 9·05%).

NN'-Dibenzoyl-α-hydroxyiminomalonamide.—Treating a solution of *NN'*-dibenzoylmalonamide (3·1 g.) in acetic acid (100 ml.) with sodium nitrite (0·7 g.) in water (5 ml.) gave an almost immediate precipitate; an equal volume of water was added and the solid filtered off; *NN'-dibenzoyl-α-hydroxyiminomalonamide* (2·7 g.) separated from ethanol (*ca.* 200 ml.) as laths, m. p. 180° (effervescence) (Found: C, 60·2; H, 3·8; N, 12·3. $C_{17}H_{13}O_5N_3$ requires C, 60·15; H, 3·85; N, 12·4%).

Hydrogenation. The compound (1 g.) in ethanol (50 ml.) with Adams platinum catalyst absorbed hydrogen (130 ml. Calc. for 2 mols., 132 ml.) during 1 hr.; a solid precipitate remained and was crystallised from an excess of water; *α-amino-NN'-dibenzoylmalonamide* (0·65 g.) was obtained as laths, m. p. 205° (decomp.) (Found: C, 62·95; H, 4·55; N, 13·15. $C_{17}H_{14}O_4N_2$ requires C, 62·75; H, 4·65; N, 12·9%). The amino-compound (0·5 g.) was boiled with N-sodium hydroxide (10 ml.) for 2 min.; the cooled solution was acidified with acetic acid to precipitate *5-N-benzoylcarbamoyl-4:5-dihydro-4-oxo-2-phenylglyoxaline* which separated from acetic acid as needles, m. p. >300° (0·35 g.) (Found: C, 65·3; H, 4·1; N, 14·05. $C_{17}H_{13}O_3N_3$ requires C, 66·1; H, 4·25; N, 13·7%).

Bromination of N-(Cyanoacetyl)benzamide.—To a solution of *N*-(cyanoacetyl)benzamide (1·88 g.) in warm acetic acid (50 ml.) was added bromine (1·6 g.); the halogen was rapidly absorbed and hydrogen bromide was freely evolved. The solution was cooled, and water (200 ml.) added until the solution was opalescent; when this was kept overnight a colourless solid separated; the *dibromo-compound* (1·3 g.) crystallised from ethanol as prisms, m. p. 140° (Found: C, 34·0; H, 2·25; N, 8·0. $C_{10}H_6O_2N_2Br_2$ requires C, 34·6; H, 1·7; N, 8·1%).

N-Benzoyl-α-cyano-β-ethoxyacrylamide.—*N*-(Cyanoacetyl)benzamide (6·9 g.), ethyl orthoformate (5·7 g.), and acetic anhydride (8 g.) were boiled under reflux for 1 hr.; the crystals which separated on cooling were filtered off and washed with a little ethanol; the *ethoxy-compound*

(5 g.) crystallised from ethanol as needles, m. p. 143° (Found: C, 63·25; H, 4·7; N, 11·55. $C_{13}H_{12}O_2N_2$ requires C, 63·9; H, 4·95; N, 11·45%). Hydrolysis of the amide with N-sodium hydroxide gave ammonia, carbon dioxide, benzoic acid, and cyanoacetaldehyde (2 : 4-dinitrophenylhydrazone).

β-Anilino-N-benzoyl-α-cyanoacetamide.—To a solution of the ethoxy-amide (0·2 g.) in warm ethanol (5 ml.) was added aniline (1 or 2 drops). Cooling gave the crystalline *anilino-amide* (0·15 g.) which separated from ethanol as needles, m. p. 180° (Found: C, 69·9; H, 4·35; N, 14·45. $C_{17}H_{15}O_2N_3$ requires C, 70·1; H, 4·5; N, 14·45%).

N-Benzoyl-α-cyano-β-phenylhydrazinoacrylamide.—The ethoxy-amide (0·5 g.) and phenylhydrazine (0·3 g.) in warm ethanol (5 ml.) gave an orange-yellow solution which when cooled soon gave the crystalline *phenylhydrazino-amide* (0·25 g.) which separated from ethanol as needles, m. p. 155° (Found: C, 66·3; H, 4·6; N, 18·25. $C_{17}H_{14}O_2N_4$ requires C, 66·65; H, 4·6; N, 18·3%).

5-Cyano-1 : 2 : 3 : 4-tetrahydro-4-oxo-2-phenylpyrimidine.—*N*-Benzoyl-α-cyano-β-ethoxyacrylamide (0·5 g.) was treated with 1% aqueous ammonia (20 ml.); the amide soon dissolved when the suspension was shaken and set aside for a short time; acidification with acetic acid then precipitated the *phenylpyrimidine* (0·35 g.) which crystallised from ethanol as needles, m. p. 295—297° (Found: C, 66·4; H, 3·4; N, 21·1. Calc. for $C_{11}H_7ON_3$: C, 67·0; H, 3·6; N, 21·3%); Mitter and Palit (*J. Indian Chem. Soc.*, 1925, **2**, 61) give m. p. 295°.

Reaction of Cyanoacetic acid, Ethyl Orthoformate, Acetic Anhydride, and Amides.—(*a*) Cyanoacetic acid (8·5 g.), acetamide (6·1 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) were boiled under reflux for 1 hr. The clear pale brown solution was evaporated to a small volume *in vacuo* to give a syrup which soon crystallised; *ethyl acetamidomethylenecyanoacetate* (5·6 g.) separated from light petroleum as needles, m. p. 95—96° (Found: C, 52·8; H, 5·3; N, 15·5%); hydrolysis with N-sodium hydroxide gave ammonia, carbon dioxide, and cyanoacetaldehyde. The ester (1 g.) was boiled with aqueous methylamine (10 ml.; 25%) for 10 min.; the solution was cooled and the solid collected; *ethyl α-cyano-N-methylaminomethyleneacetate* (0·6 g.) separated from water as plates or needles, m. p. 75° (Found: C, 54·6; H, 6·45; N, 18·3. $C_7H_{10}O_2N_2$ requires C, 54·55; H, 6·5; N, 18·1%).

(*b*) Cyanoacetic acid (8·5 g.), urethane (8·9 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) were boiled together under reflux and the solution evaporated to a syrup *in vacuo*; this was stirred with cold water (100 ml.) to give a crystalline residue admixed with oil; the solid was readily separated by filtration; *ethyl α-cyano-N-ethoxycarbonylaminomethyleneacetate* (4·5 g.) crystallised from water as needles, m. p. 114—115° (Found: C, 51·3; H, 5·75; N, 13·4%); treatment of this compound with N-sodium hydroxide and with methylamine gave the same results as in the preceding experiment.

(*c*) Cyanoacetic acid (8·5 g.), benzamide (12·1 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) similarly gave *ethyl benzamidomethylenecyanoacetate* (8 g.) which crystallised from ethanol as laths, m. p. 113—114° (Found: C, 64·1; H, 4·75; N, 11·6%); hydrolysis with N-sodium hydroxide gave ammonia, carbon dioxide, cyanoacetaldehyde, and benzoic acid, and treatment of the ester with methylamine gave the same result as recorded in (*a*) and (*b*). The ester (0·5 g.) slowly dissolved in concentrated aqueous ammonia; the solution eventually deposited benzamide, m. p. and mixed m. p. 120°.

Reaction of Ethyl α-Cyano-α-ethoxymethyleneacetate with Amides.—This ester (0·24 g.) and acetamide (0·1 g.) were heated at 140—150° (bath) for 30 min. to give a clear pale brown melt which crystallised when cooled; ethyl acetamidomethylenecyanoacetate (0·15 g.) separated from ethanol–water as needles, m. p. 95° not depressed with the compound prepared as above. Analogous compounds were obtained when acetamide was substituted for benzamide or urethane and the compounds so obtained did not depress the m. p.s of the corresponding substances prepared as above.

Reaction of Ethyl α-Cyano-α-ethoxymethyleneacetate with Methylamine.—The ester (1 g.) was treated with aqueous methylamine (5 ml.; 28%); a clear solution was rapidly obtained which deposited ethyl α-cyano-*N*-methylaminomethyleneacetate (0·8 g.) which separated from water as plates or needles, m. p. 75°, and the m. p. was not depressed when admixed with the compound prepared as above.

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UNIVERSITY OF TECHNOLOGY, SYDNEY, N.S.W., AUSTRALIA. [*Received, January 19th*, 1955.]

Synthetic Experiments in the cyclo*Heptatrienone Series. Part VI.* Further Reactions of 3-Hydroxytropone.*

By A. W. Johnson and M. Tišler.

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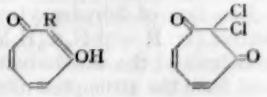
Reaction of 3-hydroxytropone with electrophilic reagents leads to substitution in the 2-position of the ring and 2-iodo-, 2-chloro-, 2-nitro-, 2-amino-, and 2-*p*-tolylazo-derivatives have been prepared. Dichlorination leads to a non-aromatic 1 : 3-diketonic derivative. The Sandmeyer reaction with 2-amino-3-hydroxytropone gives the 2-chloro-compound.

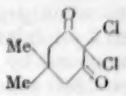
In Part IV (Johns, Johnson, and Tišler, *J.*, 1954, 4604) the preparation of 3-hydroxytropone (I; R = H) was described and it was of interest to compare the reactivity and stability of tropolone with those of 3-hydroxytropone where intramolecular hydrogen bonding between the hydroxyl and the carbonyl group does not exist. It is known that the stability of tropone itself is not as great as that of tropolone although both are derivatives of the aromatic *cyclo*heptatrienylium (tropylium) cation and thus the five-membered hydrogen-bonded ring in tropolone makes a significant contribution to its stability. The absence of intramolecular hydrogen bonding in 3-hydroxytropone has a marked effect on its physical properties (Part IV, *loc. cit.*) for the isomer is less volatile than tropolone, is more acidic, has a considerably higher m. p. (179—180°; tropolone 49°), and is insoluble in non-polar solvents.

The chemical reactions of tropolone, especially electrophilic substitutions and ring contractions to benzenoid compounds, have been studied in detail (review: Johnson, *J.*, 1954, 1331), particularly by Nozoe and his co-workers, but little has been reported so far on similar reactions with tropones lacking the 2-hydroxyl group.



(I)

(II)



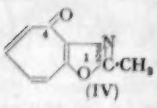
(III)

In 3-hydroxytropone (I; R = H) the combined directive influence of the two oxygen atoms renders the 2-position most favourable for electrophilic attack and it was found that bromination even in the presence of a moderate excess of bromine yielded the 2-bromo-derivative (I; R = Br), the structure of which was proved by *X*-ray examination and by conversion into the known 3-hydroxytropolone (I; R = OH) (Part IV, *loc. cit.*). Iodination of 3-hydroxytropone in acetic acid gave 3-hydroxy-2-iodotropone (I; R = I) although this derivative was not obtained by reaction with iodine in aqueous potassium iodide or from an attempted halogen exchange with the bromo-compound. The introduction of chlorine into a cooled solution of 3-hydroxytropone in acetic acid rapidly gave the colourless 2-chloro-derivative (I; R = Cl) which with diazomethane yielded the corresponding methyl ether. Both of these 2-chlorotropones have been prepared from 7-bromotropolone by Seto (*Sci. Rep. Tôhoku Univ.*, 1953, **37**, 275, 377). A yellow dichloro-compound, $C_7H_4O_2Cl_2$, was isolated as a by-product from the low-temperature chlorination of 3-hydroxytropone and it was the major product when the chlorination was carried out in warm carbon tetrachloride solution. It was also obtained in rather poor yield from the further chlorination of 2-chloro-3-hydroxytropone and reduction of the dichloro-compound with stannous chloride in acetic acid gave a small yield of the original monochloro-derivative. No pure product was isolated from a reduction of the dichloro-compound with zinc and acetic acid. The ultraviolet and infrared spectra indicated that the dichloro-compound no longer contained a tropone ring and the compound is probably represented as (II), 2 : 2-dichloro*cyclo*hepta-4 : 6-diene-1 : 3-dione. It formed a yellow solution in aqueous sodium

* Part V, *J.*, 1955, 309.

hydroxide but was decomposed when the solution was warmed. The formation of (II) is paralleled by the reaction of chlorine with other cyclic β-diketones, *e.g.*, dihydro-5 : 5-dimethylresorcinol gives (III) (Hirst and Macbeth, *J.*, 1922, **121**, 2169), but other attempts to simulate typical β-diketone reactions, *e.g.*, condensation with benzaldehyde, were negative. As with tropolone (Sebe *et al.*, *Proc. Japan Acad.*, 1952, **28**, 282; 1953, **29**, 107, 110) the Diels–Alder addition of maleic anhydride to 3-hydroxytropone did not occur except under forcing conditions necessary to overcome the aromatic character of the ring system. When the reactants were heated together at 100—120° in a sealed tube a dicarboxylic acid was obtained in small yield, which was probably an *exo*-adduct as there was no evidence of lactone formation even after repeated sublimation.

Attempted nucleophilic displacements of the halogen atoms in 2-bromo(or chloro)-3-hydroxytropone by cyanide or thiol groups were unsuccessful, as were experiments designed to bring about further electrophilic substitution, *e.g.*, diazonium coupling, nitration, and bromination. The alkaline ring contractions of 2-bromo-3-hydroxytropone as well as of 3-hydroxytropone itself were discussed in Part IV (*loc. cit.*) but at present 3-hydroxytropolone (I; R = OH) is the only compound of the general structure (I) which gives salicylic acid on alkaline rearrangement. Nitration of 3-hydroxytropone with a cooled mixture of nitric and sulphuric acid gave the pale yellow 2-nitro-derivative (I; R = NO_2). With a nitric–acetic acid mixture, the hydrobromide of 3-hydroxytropone gave the 2-bromo-derivative and from a similar reaction with the free base unchanged material was obtained. Hydrogenation of the nitro-compound in the prseence of Raney nickel yielded 2-amino-3-hydroxytropone (I; R = NH_2) which formed pale yellow needles and gave a crystalline sulphate. Acetylation of the amino-derivative with acetic anhydride gave a compound $C_9H_7O_2N$, probably the substituted oxazole (IV), formed by loss of acetic acid from the expected *ON*-diacetyl derivative. A Sandmeyer reaction on diazotised 2-amino-3-hydroxytropone gave the 2-chloro-compound, identical with that obtained from the direct chlorination of 3-hydroxytropone and thus confirmed the assigned position of the nitro-group in the nitration product. Reaction of 3-hydroxytropone with diazotised *p*-toluidine gave the red 2-*p*-tolylazo-derivative (I; R = *p*-$N_2 \cdot C_6H_4Me$) but an attempt to obtain the 2-amino-compound by hydrogenolysis of the azo-derivative was unsuccessful. No pure substitution products were obtained from the attempted nitrosation, sulphonation (with sulphamic acid), amination (with hydroxylamine), or hydroxylation (with potassium persulphate) of 3-hydroxytropone.


(IV)

Of the substitution products of 3-hydroxytropone which still retain the tropone ring those obtained so far are monosubstituted and have the substituent in the 2-position, except for 7-bromo-3-hydroxytropone (Part IV, *loc. cit.*), prepared by an indirect method, and it is of interest that in the one case, chlorination, where disubstitution of 3-hydroxytropone did occur, the aromatic ring system was destroyed. Orientation of the substitution products, as with the tropolones, by employing the alkaline rearrangement to derivatives of benzoic acid is not so useful in the 3-hydroxytropone series as many side reactions occur (Part IV, *loc. cit.*), and the orientations have been carried out by relating the products to the 2-bromo-derivative, the structure of which is known with certainty. With the exception of halogenation the experimental conditions required for the substitution reactions of 3-hydroxytropone are more critical than in the tropolone series because of the decreased stability of the parent compound and of the products.

Experimental

Ultraviolet spectra were determined in 95% EtOH and infrared spectra on Nujol mulls except where otherwise stated.

3-Hydroxy-2-iodotropone.—3-Hydroxytropone (200 mg.) was suspended in glacial acetic acid (3 c.c.), and a solution of iodine (228 mg., 1·1 mol.) in acetic acid (15 c.c.) added to it. The mixture was heated on the water-bath for 10 min. and, after cooling, water (80 c.c.) was added and the whole kept overnight. The precipitated iodo-compound was separated and crystallised from ethanol, forming brownish needles (170 mg.), m. p. 163—164° (decomp.) (Found: C, 34·3;

H, 2·4; I, 50·8. $C_7H_5O_2I$ requires C, 33·9; H, 2·05; I, 51·2%). Light absorption: max. at 251, 312, 324, 360 mμ (log ε 4·29, 3·69, 3·63, and 3·58 respectively); in 0·1 N-sodium hydroxide: max. at 260, 311, 322, and 365—366 mμ (log ε 4·40, 3·76, 3·69, and 3·54 respectively). The infrared spectrum showed max. at 1637, 1534, 1515, 1410, 1364, 1272, 1258, 1214, 1036, 1015, 862, 835, 793, and 684 cm.$^{-1}$. The product could be sublimed at 140°/0·5 mm. but considerable decomposition ensued.

2-Chloro-3-hydroxytropone and 2 : 2-Dichloro-4 : 6-cycloheptadiene-1 : 3-dione.—Chlorine was passed into a cooled (ice) solution of 3-hydroxytropone (195 mg.) in acetic acid (15 c.c.). The precipitate which was obtained at once was separated and crystallised from methanol, as colourless needles (226 mg., 88%), m. p. 210—215° (decomp.) [Seto, *loc. cit.*, gives m. p. 210—215° (decomp.)] (Found: C, 53·4; H, 3·6. Calc. for $C_7H_5O_2Cl$: C, 53·7; H, 3·2%). Light absorption: max. at 213, 254, 260, 274, and 310 mμ (log ε 4·10, 4·50, 4·52, 4·38, and 3·96 respectively); in 0·1N-sodium hydroxide: max. at 260, 270, and 308 mμ (log ε 4·51, 4·46, and 3·83 respectively) with an inflection at 340—354 mμ (log ε 3·40). Infrared spectrum: max. at 1645, 1538, 1527, 1420, 1311, 1282, 1266, 1227, 1049, 1036, 985, 920, 840, 799, 685, and 652 cm.$^{-1}$. A determination on a mull in hexachlorobutadiene showed additional bands at 1468 and 1379 cm.$^{-1}$.

Treatment of 2-chloro-3-hydroxytropone with diazomethane gave 2-chloro-3-methoxytropone which, after sublimation at 100°/0·5 mm. and crystallisation from ether–light petroleum (b. p. 40—60°) formed colourless crystals, m. p. 100—101° (Seto, *loc. cit.*, gives m. p. 102—103°) (Found: C, 56·45; H, 4·4. Calc. for $C_8H_7O_2Cl$: C, 56·3; H, 4·15%). Light absorption: max. at 217, 256, 264, 312, and 324 mμ (log ε 4·08, 4·41, 4·36, 3·69, and 3·65 respectively). The infrared spectrum showed max. at 1642, 1570, 1416, 1247, 1225, 1172, 1149, 1082, 1025, 936, 917, 866, 830, 797, and 789 cm.$^{-1}$. A determination on a hexachlorobutadiene mull showed additional maxima at 1477 and 1453 cm.$^{-1}$.

Evaporation of the mother-liquors from the crystallisation of 2-chloro-3-hydroxytropone gave a solid residue which after sublimation at 75°/0·5 mm. gave a yellow crystalline product, m. p. 83°. Larger quantities (56%) of this material, *2 : 2-dichlorocyclohepta-4 : 6-diene-1 : 3-dione*, were obtained together with smaller amounts (23%) of 2-chloro-3-hydroxytropone when 3-hydroxytropone was chlorinated in carbon tetrachloride solution at 50°. The dichloro-compound formed bright yellow plates, m. p. 83°, after crystallisation from ether–light petroleum (b. p. 40—60°) (Found: C, 43·7; H, 2·4. $C_7H_4O_2Cl_2$ requires C, 44·0; H, 2·1%). Light absorption: max. at 286—288 mμ (log ε 3·84). Infrared spectrum: max. at 1704, 1686, 1631, 1595, 1420, 1282, 1198, 1127, 1010, 992, 959, 905, 883, 869, 787, and 726 cm.$^{-1}$. The same compound was also obtained (26%) from the chlorination of 2-chloro-3-hydroxytropone in carbon tetrachloride at 50°. It formed no precipitate with ethanolic silver nitrate and gave no ferric reaction, but liberated iodine from aqueous potassium iodide. The solution in cold aqueous sodium hydroxide was yellow but it rapidly darkened and decomposed on warming. On hydrogenation over platinum, 6·35 mols. of hydrogen were absorbed. Treatment with stannous chloride in glacial acetic acid (cf. Vorländer and Kohlmann, *Annalen*, 1902, **322**, 257) gave a small amount of 2-chloro-3-hydroxytropone.

3-Hydroxy-2-nitrotropone.—Nitric acid (*d* 1·42; 0·5 c.c.) was added dropwise to a cooled solution of 3-hydroxytropone (0·5 g.) in concentrated sulphuric acid (5 c.c.), and the mixture kept overnight. It was poured on ice (5 g.) and the yellow precipitate separated, dried, and extracted with ether. Concentration of the ethereal solution gave small pale yellow needles, m. p. 258—260° (decomp.) (0·38 g., 56%) (Found: C, 50·4; H, 3·4; N, 8·4. $C_7H_5O_4N$ requires C, 50·3; H, 3·0; N, 8·4%). Light absorption: max. at 213—214, 246, and 298—299 mμ (log ε 4·22, 4·47, and 3·62 respectively) with an inflection at 326—333 mμ (log ε 3·35); in 0·1N-sodium hydroxide: max. at 254 and 291 mμ (log ε 4·50 and 3·70 respectively). Infrared spectrum: max. at 1645, 1603, 1534, 1289, 1266, 1244, 1220, 1070, 1048, 990, 948, 843, 808, 689, and 651 cm.$^{-1}$. A determination on a mull in hexachlorobutadiene also showed bands at 1462 and 1379 cm.$^{-1}$. The *nitro-compound* was very soluble in acetone, soluble in alcohol and acetic acid, sparingly soluble in ether, and insoluble in *cyclo*hexane or light petroleum. It could be sublimed at 190°/0·5 mm. but the process was attended by considerable decomposition.

2-Amino-3-hydroxytropone.—An ethanolic solution of the foregoing nitro-compound (167 mg.) was hydrogenated in the presence of Raney nickel, and the reaction stopped after the absorption of the theoretical ($NO_2 \longrightarrow NH_2$) volume of hydrogen. The catalyst was separated, the solvent evaporated, and the residue made just alkaline with 2N-sodium hydroxide. After separation of any solid material the red solution was acidified with acetic acid, a yellow precipitate being obtained which was crystallised from water to give small yellow needles of *base*

(112 mg., 82%), m. p. 228° (decomp.) (Found : C, 61·05; H, 4·95; N, 10·3. $C_7H_7O_2N$ requires C, 61·3; H, 5·15; N, 10·2%). Light absorption : max. at 248, 262, 272, 336, and 409 mμ (log ε 4·48, 4·26, 4·28, 4·13, and 4·08 respectively); in 0·1N-sodium hydroxide : max. at 216, 260, 277, 342, and 413 mμ (log ε 4·13, 4·46, 4·32, 4·07, and 3·94 respectively). The infrared spectrum showed max. at 3448, 3300, 1595, 1536, 1499, 1399, 1274, 1235, 1198, 1156, 847, 784, and 763 cm.$^{-1}$ An additional band at 2915 cm.$^{-1}$ was revealed when the determination was carried out on a mull in hexachlorobutadiene. The amine gave a purple ferric reaction, and formed a crystalline *sulphate*, m. p. 247° (decomp.) (from water) (Found : C, 45·2; H, 4·4. $C_{14}H_{16}O_8N_2S$ requires C, 45·2; H, 4·3%). Light absorption : max. at 249, 272, 335, 386, and 410 mμ (log ε 4·77, 4·41, 4·31, 4·19, and 4·18 respectively), with an inflection at 260—264 mμ (log ε 4·48). Infrared spectrum : max. at 3413, 3175, 2469, 1610, 1585, 1529, 1316, 1294, 1274, 1227, 1034, 847, 782, and 728 cm.$^{-1}$. A determination on a mull in hexachlorobutadiene showed additional max. at 2899, 2740, 1456, and 1379 cm.$^{-1}$.

Sandmeyer Reaction with 2-Amino-3-hydroxytropone.—A diazotised solution of 2-amino-3-hydroxytropone sulphate (184 mg.) was added dropwise to an ice-cold solution of cuprous chloride (100 mg.) in hydrochloric acid. After being stirred at 0° for 10 min. the product was heated to 30—35° on the water-bath. The precipitate which was obtained was separated and crystallised from methanol, as colourless needles (78 mg., 64%), m. p. 210—212° (decomp.), not depressed on admixture with an authentic sample of 2-chloro-3-hydroxytropone.

Acetylation of 2-Amino-3-hydroxytropone.—The base (100 mg.) was heated under reflux with fused sodium acetate (0·5 g.) and acetic anhydride (5 c.c.) for 1 hr. The product was cooled, diluted with water (50 c.c.), and continuously extracted with ether for 2 days. Removal of the ether from the dried extract gave a residue which was sublimed at 140°/0·5 mm. to give colourless crystals (32 mg.), m. p. 153°, of *2-methyl-4-oxocycloheptaoxazole* (Found : C, 66·7; H, 4·2; N, 8·75. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%). Light absorption : max. at 228, 307, and 334 mμ (log. ε 4·35, 3·89, and 3·87 respectively) with an inflection at 344—347 mμ (log ε 3·80). The infrared spectrum showed max. at 1626, 1590, 1575, 1527, 1272, 1250, 1212, 1151, 1078, 1063, 1036, 964, 946, 875, 847, 813, 777, 719, and 682 cm.$^{-1}$. A small quantity of a second substance, m. p. 139°, was isolated from the crystallisation but the amount obtained was insufficient to permit identification.

3-Hydroxy-2-p-tolylazotropone.—*p*-Toluidine (300 mg.) was diazotised and added to an alkaline solution of 3-hydroxytropone (370 mg.) and the mixture kept for ½ hr. It was then acidified with glacial acetic acid, and the solid separated. For purification it was dissolved in a small volume of cold 3N-sodium hydroxide, the solution filtered, and the filtrate diluted with water (5 c.c.) and acidified with 3N-hydrochloric acid. The *azo-compound* was obtained as small red needles (127 mg.), m. p. 154°. The purification was repeated before analysis (Found : N, 11·6. $C_{14}H_{12}O_2N_2$ requires N, 11·7%).

Reaction of 3-Hydroxytropone with Maleic Anhydride.—3-Hydroxytropone (0·122 g.) and freshly distilled maleic anhydride (0·1 g.) were heated together in a sealed tube at 100—120° for 6 hr. The product was dissolved as far as possible in 3N-sodium hydrogen carbonate solution, and the neutral material extracted into ether. The aqueous layer was acidified and continuously extracted with ether for 2 days. The solvent was removed from the dried ethereal extract, and the solid residue sublimed twice at 170°/0·5 mm., being obtained as a colourless solid (28 mg., 12%) (Found : C, 55·5; H, 4·0. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%).

Grateful acknowledgment is made to the British Council for a Scholarship (to M. T.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 26th*, 1955.]

The Orton Rearrangement. Part I. Preparation and Properties of N-Bromo- and N-Chloro-2 : 6-dimethylacetanilide.

By M. J. S. Dewar and J. M. W. Scott.

[Reprint Order No. 6070.]

N-Bromo- and *N*-chloro-2 : 6-dimethylacetanilide have been prepared, and their reactions studied with a view to kinetic experiments later. Both substances substantially conform to the usual behaviour of *N*-halogenoacylanilides.

In connection with the Orton rearrangement of *N*-halogenoacylanilides, Dewar ("The Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949) suggested that it would be of interest to prepare *N*-bromo-2 : 6-dimethylacetanilide and study its properties, especially the rate of rearrangement. With a view to kinetic studies, the two compounds named in the title have been prepared, and their respective reactions investigated.

The *N*-bromo-compound has been rearranged in boiling water, in acetic acid, and with trichloroacetic acid in chlorobenzene (aprotic conditions). In all cases a substantial yield of the expected 4-bromo-compound was obtained but in acetic acid some 3-bromo-compound may also have been formed.

The *N*-bromo-compound was treated with sulphuric acid in acetic anhydride in the dark, in daylight, and in ultraviolet light. In each case the *N*-bromo-amide disappeared but the only product isolated was the unsubstituted amide. One case was, however, exceptional; after the *N*-bromo-compound had been left in acetic anhydride and sulphuric acid for some time a different product was obtained, the analysis of which indicated that the *N*-bromo-2 : 6-dimethylacetanilide had isomerised; as its m. p. differed from those of 3- and 4-bromo-2 : 6-dimethylacetanilide and *N*-bromoacetyl-2 : 6-dimethylaniline, the only possible structure for the compound appears to be (I), formed by internal bromination of one of the substituent methyl groups. This reaction could not be repeated, perhaps indicating that it involved some free-radical process.

(I)

The bromine in the compound (? I) was singularly unreactive, not being removed by alcoholic silver nitrate or by hot sodium hydroxide. This inertness might be expected, since S_N2 reactions would be sterically inhibited, and since S_N1 reactions would be sterically hindered in the sense that the methylene group of the intermediate carbonium ion would be initially perpendicular to the ring.

In the preparation of *N*-bromoacetyl-2 : 6-dimethylaniline it was not found possible to acylate 2 : 6-dimethylaniline in pyridine with bromoacetyl bromide. The reaction of propionyl chloride with the amine was investigated to ascertain whether steric factors were affecting the reaction. In this case, however, a good yield of 2 : 6-dimethylpropionanilide was obtained.

*cyclo*Hexene was readily brominated in the α-position with *N*-bromo-2 : 6-dimethylacetanilide in the presence of benzoyl peroxide as a catalyst. Steric factors should facilitate this particular reaction, since the loss of the bromine atom would yield a less hindered radical.

The *N*-chloro-compound, on treatment with the same rearranging reagents as the *N*-bromo-compound, gave what were assumed to be mixtures of isomers, *i.e.*, 3- and 4-chloro-2 : 6-dimethylacetanilide, together with a small loss of halogen to the solvent. It was not possible to separate these mixtures by chromatography or fractional crystallisation. Boiling water, however, seems to give only the 4-chloro-compound. The reason for this is not easy to see, although it has been previously reported that the orientation in the chlorination of anilides is somewhat dependent on the solvent used.

Experimental

2 : 6-Dimethylacetanilide was prepared from the corresponding amine and acetic anhydride. It was crystallised once from aqueous alcohol and had m. p. 178° (lit., 177°).

N-Bromo-2 : 6-dimethylacetanilide.—A mixture of 2 : 6-dimethylacetanilide (20 g.) and

potassium hydrogen carbonate (20 g.) was thoroughly powdered and added to distilled water (*ca.* 3000 ml.) with vigorous stirring. The suspension formed was cooled to 0° and treated (30 min.) with cold hypobromous acid (2 mol.) with constant stirring. Stirring was continued for a further 15 min. and the pale yellow solid which had formed was collected, washed with cold distilled water, and dried *in vacuo*. It crystallised from chloroform–light petroleum (b. p. 40—60°) in yellow prisms, m. p. 122—123° (18 g., 60%) (Found : active Br, 32·8. $C_{10}H_{12}ONBr$ requires Br, 33·0%).

Rearrangements. (1) In boiling water. Pure N-*bromo*-2 : 6-*dimethylacetanilide* (1 g.) was added to boiling distilled water (*ca.* 50 ml.). The *N*-bromo-compound melted, forming globules which eventually solidified. The solid crystallised from absolute methanol in needles, m. p. 194—195°. Beilstein's " Handbuch " gives m. p. 193° for 4-bromo-2 : 6-dimethylacetanilide.

(2) In acetic acid. The pure *N*-bromo-acetanilide (10 g.) was dissolved in " AnalaR " glacial acetic acid (*ca.* 50 ml.), and the solution left in the dark until it no longer liberated iodine from acid potassium iodide solution (*ca.* 28 days). The acetic acid solution was then poured on ice, and the precipitate (9·5 g.) collected, washed, dried, and weighed (Found : Br, 32·7, 32·6. Calc. for $C_{10}H_{12}ONBr$: Br, 33·0%). It crystallised from absolute methanol in needles, m. p. 192—194° (7·1 g.). The mother-liquors yielded a solid which was not separated into pure components by chromatography or fractional crystallisation. If a solution of the *N*-bromo-compound in acetic acid was warmed, free bromine was liberated.

(3) Aprotic conditions. Pure *N*-bromo-2 : 6-dimethylacetanilide (5 g.) was dissolved in a 0·6N-solution of " AnalaR " trichloroacetic acid in pure chlorobenzene (*ca.* 25 ml.), and the solution left in the dark as in (2), *i.e.*, for *ca.* 28 days. The crystals that separated, when collected and washed with light petroleum (b. p. 40—60°), had m. p. 194°. Chloroform was added to the filtrate, and the acid removed by washing with potassium hydrogen carbonate solution. The non-aqueous layer was then dried, and the bulk of the solvent removed under reduced pressure. A further yield of solid, m. p. 193°, was obtained by addition of light petroleum (b. p. 40—60°). The total yield of solid was 4·2 g.

(4) In sulphuric acid and acetic anhydride. Three solutions of pure *N*-bromo-2 : 6-dimethylacetanilide (8 g.) in a mixture of concentrated sulphuric acid and acetic anhydride (30 ml.; 10% H_2SO_4 by vol.) were left respectively in the dark, in daylight, and in ultraviolet light, until they no longer liberated iodine from acid potassium iodide solution. In each case, the solution was then poured on ice, and the precipitated solid collected, washed, dried, and weighed; a portion of the solid was then crystallised from aqueous alcohol and tested qualitatively for bromine, with negative results. The yields, m. p.s, and mixed m. p.s with authentic 2 : 6-dimethylacetanilide were as below :

Conditions	Wt. (g.)	M. p.	Mixed m. p.	Conditions	Wt. (g.)	M. p.	Mixed m. p.
Dark	3·9	177°	177°	U.V. light ...	4·2	177—178°	177°
Daylight	4·1	177—178°	177				

Exceptional case. Pure *N*-bromo-2 : 6-dimethylacetanilide (1 g.) was dissolved in a solution of concentrated sulphuric acid in acetic anhydride (10 ml.; 10% H_2SO_4 by vol.), and the resulting solution left in daylight until it no longer liberated iodine from acid potassium iodide solution. The solution was then poured on ice, forming fine needles, m. p. 128—129° (from aqueous alcohol) (Beilstein gives the m. p.s of 3- and 4-bromo-2 : 6-dimethylacetanilide as 136° and 193°, respectively) (Found : C, 49·3; H, 4·9; N, 5·6; Br, 33·3. Calc. for $C_{10}H_{12}ONBr$: C, 49·6; H, 5·0; N, 5·8; Br, 33·0%).

N-*Bromoacetyl*-2 : 6-*dimethylaniline*.—Bromoacetyl bromide (8·3 g., 1 mol.) was added dropwise to 2 : 6-dimethylaniline (10 g., 2 mol.). The mixture became brown and then solidified. The product was boiled with " Norit " and methanol and then crystallised from methanol (6·3 g., 59%). Further crystallisation from methanol gave needles, m. p. 150—151° (Found : C, 49·3; H, 5·1; N, 6·1; Br, 33·3. $C_{10}H_{12}ONBr$ requires C, 49·6; H, 5·0; N, 5·8; Br, 33·0%).

2 : 6-*Dimethylpropionanilide*.—Propionyl chloride (1·5 ml.) was added dropwise to a cooled solution of 2 : 6-dimethylaniline (1 g.) in dry pyridine (5 g.) with constant stirring. The resulting solution was poured into excess of dilute hydrochloric acid, and the precipitate collected, washed, dried, and weighed (1·3 g., 80%). A portion, crystallised from absolute methanol and then light petroleum (b. p. 80—100°), formed needles, m. p. 121° (Found : C, 74·6; H, 8·6; N, 7·7. $C_{11}H_{15}ON$ requires C, 74·5; H, 8·5; N, 7·9%).

Bromination of cyclo*Hexene*.—Pure *N*-bromo-2 : 6-dimethylacetanilide (2 g.) was dissolved in purified *cyclo*hexene (*ca.* 50 ml.), and a trace of benzoyl peroxide added. The solution was gently refluxed, the colour changing from yellow to red (cf. *N*-bromosuccinimide brominations)

with the separation of solid. When the solution no longer liberated iodine from acid potassium iodide solution, it was cooled, and the solid collected (m. p. 177°). The bulk of the unchanged *cyclo*hexene was removed by distillation, light petroleum (b. p. 40—60°) added, and the solution chromatographed on alumina to remove the last traces of 2 : 6-dimethylacetanilide. The light petroleum was removed, leaving a small bulk of pleasant-smelling liquid (3-bromo*cyclo*hexene smells of geraniums), which was converted into 3-cyclo*hexenylthiuronium picrate* by the usual method and this was crystallised from acetone and light petroleum (b. p. 40—60°) giving yellow blades, m. p. 160—161° (Found : C, 40·3; H, 3·9; N, 18·2; S, 8·1. $C_{13}H_{15}O_7N_5S$ requires C, 40·5; H, 3·9; N, 18·2; S, 8·3%).

N-Chloro-2 : 6-dimethylacetanilide.—Pure 2 : 6-dimethylacetanilide (10 g.) was thoroughly powdered with potassium hydrogen carbonate (10 g.), the mixture added to distilled water (2 l.), and the resulting suspension cooled (*ca.* 8°). A fresh solution of sodium hypochlorite (2 mol.), likewise cooled, was then added to the suspension with vigorous stirring. The solution eventually became turbid and after 1 hr. the *chloro-compound* formed was collected, washed, and dried. It crystallised from chloroform and light petroleum (b. p. 40—60°) on strong cooling in blades (6·3 g., 52%), m. p. 112—113° (Found : active Cl, 17·8. $C_{10}H_{12}ONCl$ requires Cl, 17·9%).

Rearrangements. (1) In boiling water. Pure *N*-chloro-2 : 6-dimethylacetanilide (1 g.) was added to boiling distilled water (*ca.* 50 ml.). The water became yellow and smelt of chlorine. When the reaction was complete the mixture was cooled, and the separated solid collected and crystallised several times from aqueous alcohol. It had m. p. 194°; Beilstein records m. p. 195° for 4-chloro-2 : 6-dimethylacetanilide.

(2) In acetic acid. Pure *N*-chloro-2 : 6-dimethylacetanilide (2 g.) was dissolved in " AnalaR " glacial acetic acid (10 ml.), and the solution warmed on a steam-bath until it no longer liberated iodine from acid potassium iodide solution (*ca.* 12 hr.). It was then poured on ice, and the precipitate collected, washed, and dried (Found : Cl, 17·5. Calc. for $C_{10}H_{12}ONCl$: Cl, 17·9%). The solid, crystallised several times from aqueous alcohol, still melted over a large range, 145—155°. A portion of the solid was chromatographed on alumina by using light petroleum (b. p. 60—80°) but no separation was achieved.

(3) Aprotic conditions. Pure *N*-chloro-2 : 6-dimethylacetanilide (2 g.) was dissolved in a 0·6N-solution of " AnalaR " trichloroacetic acid in chlorobenzene (*ca.* 10 ml.), and the solution left on a steam-bath in the dark until it no longer liberated iodine from acid potassium iodide solution (*ca.* 12 hr.). Chloroform was then added, and the acid removed by washing the non-aqueous layer with potassium hydrogen carbonate solution. The non-aqueous layer was dried, and the bulk of the solvent removed under reduced pressure. Light petroleum (b. p. 40—60°) was added to the residue, and the precipitated solid collected and dried (Found : Cl, 15·5. Calc. for $C_{10}H_{12}ONCl$: Cl, 17·9%). The solid was crystallised several times from aqueous alcohol but still melted over 144—155°. Chromatography, as before, gave no separation.

One of us (J. M. W. S.) thanks Ipswich Education Committee for a maintenance grant.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, January 26th,* 1955.]

The Constituents of High-boiling Petroleum Distillates. Part II. Trimethylnaphthalenes in a Trinidad Oil.*

By W. CARRUTHERS and (in part) A. G. DOUGLAS.

[Reprint Order No. 6110.]

1 : 2 : 5-, 1 : 2 : 7-, and 2 : 3 : 6-Trimethylnaphthalene and a hydrocarbon considered to be an unknown ethylmethylnaphthalene have been isolated from a fraction of a Trinidad crude oil.

THE presence of naphthalene homologues in mineral oil fractions has been demonstrated by several groups of workers. Thus, 1- and 2-methylnaphthalene and seven of the ten dimethylnaphthalenes have been isolated from oils from various sources (see, for example, Sachanen, " The Chemical Constituents of Petroleum," Reinhold Publ. Corp., New York, 1945; Gavat and Irimescu, *Ber.*, 1941, **74**, 1812; Easterfield and McClelland, *J. Soc. Chem.*

* Part I, *J.*, 1954, 2047.

Ind., 1923, **42**, 936). Trimethylnaphthalenes (including the 2 : 3 : 6-isomer) were first unequivocally identified in a fraction from a Roumanian crude oil by Gavat and Irimescu (*Ber.*, 1942, **75**, 820) although other investigators had previously obtained them in an impure form (Markownikoff, *Annalen*, 1886, **234**, 89; Coscuig, *Petroleum Ztg.*, 1938, **34**, No. 20, 1). We have isolated the three trimethylnaphthalenes mentioned in the summary and what is probably an ethylmethylnaphthalene from a fraction of a Trinidad crude oil.

This fraction, of boiling range 267—278°, was prepared by fractional distillation of the crude oil under reduced pressure in the Chemical Engineering Laboratories of the University of Birmingham, and we are greatly indebted to Professor F. Morton for carrying out the fractionation and supplying us with the material for our investigation. The naphthalene components of the fraction were concentrated by selective extraction with furfuraldehyde (Kemp, Hamilton, and Gross, *Ind. Eng. Chem.*, 1948, **40**, 220) and reaction of the resulting aromatic-enriched extract with picric acid in ethanol. The bright red crystalline picrate obtained, on treatment with alkali, yielded an oil consisting very largely of naphthalene derivatives as shown by the ultraviolet absorption spectrum. When this material was cooled, 2 : 3 : 6-trimethylnaphthalene separated in considerable quantity and was identified by analysis, ultraviolet absorption, and oxidation with chromic acid in acetic acid to the known 2 : 3 : 6- and 2 : 6 : 7-trimethyl-1 : 4-naphthaquinone (Kruber, *Ber.*, 1939, **72**, 1972). Its abundance in our material is noteworthy. The total yield of crude hydrocarbon was 14% of the naphthalene concentrate or nearly 1% of the original distillate.

The remaining unsolidified portion of the picrate-forming material was fractionally distilled under reduced pressure, and the fractions were converted into their crystalline picrates and styphnates. By fractional crystallisation of these complexes two other trimethylnaphthalenes, a solid of m. p. 31° and a liquid, were isolated in small yield. These were identified as 1 : 2 : 5- and 1 : 2 : 7-trimethylnaphthalene respectively by comparison of the styphnates and picrates with authentic specimens. There was also obtained a small amount of another liquid hydrocarbon regarded as an unknown ethylmethylnaphthalene. Elementary analysis of the compound and its ultraviolet absorption show that it is a naphthalene hydrocarbon $C_{13}H_{14}$, but the melting points of the picrate (120—121°) and styphnate (131—133°) do not correspond with those recorded for the corresponding derivatives of any of the trimethyl-, propyl-, or *iso*propyl-naphthalenes, or of the known ethylmethylnaphthalenes. With the small amount of hydrocarbon available attempts to obtain further evidence of its structure by oxidation experiments were unsuccessful.

1 : 2 : 7-Trimethylnaphthalene has not previously been isolated from a mineral oil. Gavat and Irimescu (*loc. cit.*) claim to have obtained the 1 : 2 : 5-isomer from a Roumanian petroleum, but their identification appears open to doubt. They isolated a hydrocarbon, f. p. −5°, and assigned to it the structure of 1 : 2 : 5-trimethylnaphthalene because its picrate had the correct m. p. for this (142—143°). Two other trimethylnaphthalenes (1 : 2 : 3- and 1 : 3 : 7-), however, have picrates melting at almost the same temperature and are lower-melting than the 1 : 2 : 5-isomer which has m. p. 33·5° (Harvey, Heilbron, and Kam, *J.*, 1926, 3136; Ruzicka and Ehman, *Helv. Chim. Acta*, 1932, **15**, 140; Kruber, *Ber.*, 1939, **72**, 1972; Hewett, *J.*, 1940, 293).

Attempted fractional sulphonation of the remainder of the naphthalene concentrate, as applied by Kruber to coal tar fractions (see, for example, *Ber.*, 1939, **72**, 1972; 1940, **73**, 1174), was unsuccessful. Much tar was produced and a crystalline sulphonic acid was not obtained. Similar failure attended an attempt to isolate fluorene hydrocarbons from the non-picrate-forming part of the furfuraldehyde extract, through the 9-carboxylic acids by reaction with sodium at 100° and subsequent carboxylation. No acidic product was formed.

Experimental

Preparation of Naphthalene Concentrate.—The Trinidad distillate was a dark yellow mobile oil, b. p. 266·8—278·2°, n_D^{20} 1·5059. It constituted the fraction which ranged from 62·3 to 70·3% of the crude oil distilled. This material (10 l.) was extracted in batches (500 c.c.) by shaking with furfuraldehyde (1 l.) at room temperature for 5—6 hr. The undissolved material

from the first extraction was re-treated in the same way. Furfuraldehyde was removed on the steam-bath under reduced pressure and the dark residue distilled as a yellow oil at 110—120°/0·8 mm. (Total yield, 3400 c.c.; n_D^{20} 1·5529.) The aldehyde-insoluble oil was nearly colourless (n_D^{20} 1·4775). The distillate was treated in portions (400 c.c.) with picric acid (250 g.) in ethanol (1 l.). The red picrate was collected and the mother-liquors were repeatedly treated with picric acid (40 g.) until no more picrate separated. The later crops of picrate were contaminated with picric acid. The picrate obtained in this way from the whole of the extract was decomposed by washing its benzene solution with dilute aqueous ammonia and yielded the naphthalene concentrate as a dark oil (490 g.). This had typical naphthalene ultraviolet absorption ($\lambda_{max.}$ 270—280, 325 mμ; log $E^{1\%}_{1cm.}$ 2·36, 1·22). From the intensity at 275 mμ it was estimated that the fraction contained 89% of naphthalene compounds.

2 : 3 : 6-*Trimethylnaphthalene.*—When the oil so obtained was kept at −10° for several hours a colourless solid separated (40 g.); it crystallised from ethanol, giving 2 : 3 : 6-trimethylnaphthalene (20 g.) as plates, m. p. 100° (lit., 102°) (Found: C, 91·9; H, 8·4. Calc. for $C_{13}H_{14}$: C, 91·8; H, 8·2%), $\lambda_{max.}$ 228, 270—275, 306 (infl. 314), 320 [log ε 5·05, 3·67, 2·76, (2·56), 2·85]. The picrate formed orange needles, m. p. 126—127° (lit., 130°), and the styphnate pale yellow needles, m. p. 165° (lit., 165°). Further quantities of the hydrocarbon were obtained from the oily filtrate in ethanol (1 l.) at −70°: the crude solid (30 g.; m. p. 93°) afforded pure 2 : 3 : 6-trimethylnaphthalene, m. p. 100° on crystallisation from ethanol. Fractional crystallisation of the styphnate prepared from the mother-liquors of these crystallisations did not afford any other hydrocarbon.

The hydrocarbon, oxidised as described by Kruber (*loc. cit.*), afforded 2 : 3 : 6-, m. p. 100—101° (lit., 103°) (Found: C, 78·1; H, 6·3. Calc. for $C_{13}H_{12}O_3$: C, 78·0; H, 6·0%), and 2 : 6 : 7-trimethyl-1 : 4-naphthaquinone, m. p. 73—74° (lit., 72°) (Found: C, 78·3; H, 6·0%).

1 : 2 : 5- *and* 1 : 2 : 7-*Trimethylnaphthalene.*—The oil remaining after removal of 2 : 3 : 6-trimethylnaphthalene was fractionally distilled under reduced pressure in a column (24 in.) packed with glass helices and surrounded by an electrically heated jacket. Thirty fractions, each of about 12 g., were collected in the boiling range 80—92°/0·5 mm. These quantities were too small for successful fractional crystallisation of molecular complexes. Fractions with similar refractive indexes were accordingly recombined to give eleven larger blends.

The picrate from blended fractions 3 and 4 (25 g.; b. p. 81°/0·5 mm.; n_D^{20} 1·5740) after several crystallisations from benzene was decomposed on alumina and the recovered oil (5 g.) converted into the styphnate. Repeated crystallisation of this from ethanol raised the m. p. of the yellow needles to 154—155°, not depressed when mixed with the styphnate of 1 : 2 : 7-trimethylnaphthalene (lit., m. p. 159°). Decomposition of the pure styphnate on alumina yielded 1 : 2 : 7-trimethylnaphthalene (50 gm.), b. p. 90°/0·2 mm. (air-bath temp.) (Found: C, 91·5; H, 8·1%), $\lambda_{max.}$ 230·5, 280—285, 320, 326 mμ (log ε 5·0, 3·74, 2·56, 2·36). The picrate formed orange-red needles (from ethanol), m. p. and mixed m. p. 127—128° (lit., 129—131°) (Found: C, 56·9; H, 4·4. Calc. for $C_{13}H_{14}.C_6H_3O_7N_3$: C, 57·1; H, 4·4%).

1 : 2 : 5-Trimethylnaphthalene was obtained from fractions 23—29. In a typical experiment the picrate from the blend of fractions 23—25 (35·4 g.; b. p. 88—89°/0·5 mm.; n_D^{20} 1·6052) was crystallised twice from benzene and the oil (2·0 g.) recovered from the orange-red needles kept at −70° in ethanol solution. Scratching caused crystallisation. Further quantities were obtained from the mother-liquors. The crystals (500 mg.) were crystallised from methanol, 1 : 2 : 5-trimethylnaphthalene being obtained as colourless needles, m. p. 30—31° (lit., 33·5°) (Found: C, 91·7; H, 8·2%), $\lambda_{max.}$ 230, 275, 288 (infl. 295, 307, 311), 321 mμ [log ε 5·07, 3·78, 3·84, (3·72), (3·12), (2·92), 3·04]. The picrate formed orange-red needles, m. p. 138° (lit., 139—142°), and the styphnate orange needles or plates, m. p. and mixed m. p. 127—129° (lit., 131°) (Found: C, 55·1; H, 4·3. Calc. for $C_{13}H_{14}.C_6H_3O_8N_3$: C, 54·9; H, 4·1%).

Ethylmethylnaphthalene.—Fractions 8 and 9 were combined (26·4 g.; b. p. 84°/0·5 mm.; n_D^{20} 1·5940); the picrate was crystallised several times from benzene and the recovered oil (5·6 g.) converted into the styphnate. By repeated crystallisation from ethanol yellow needles of constant m. p. 131—133° were obtained. The hydrocarbon (80 mg.) recovered on decomposition of the styphnate crystallised at −10° but melted again at room temperature. It distilled as a colourless oil at 90°/0·3 mm. (air-bath temp.) (Found: C, 91·6; H, 8·2%), $\lambda_{max.}$ 230·5, 275, 284, (infl. 292), 320 mμ [log ε, 4·9, 3·68, 3·72, (3·26), 2·53]. The picrate formed orange-red needles (from ethanol), m. p. 119—120° (Found: N, 10·7. Calc. for $C_{13}H_{14}.C_6H_3O_7N_3$: N, 10·5%). The styphnate crystallised from ethanol in yellow needles, m. p. 131—133°, depressed to 122—125° when mixed with 1 : 2 : 5-trimethylnaphthalene styphnate (Found: N, 10·1. Calc. for $C_{13}H_{14}.C_6H_3O_8N_3$: N, 10·1%).

This work was supported by a grant from the Medical Research Council. We are greatly indebted to Professor F. Morton, University of Birmingham, for preparation of the distillate, and we thank Professors L. Ruzicka and D. H. R. Barton, F.R.S., for samples of molecular complexes of 1 : 2 : 5- and 1 : 2 : 7-trimethylnaphthalene, and Dr. J. W. Cook, F.R.S., for his interest. Microanalyses were by Miss M. Christie and Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, February 9th,* 1955.]

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*The Synthesis of Trypanocides. Part III.** 4-*Amino*-6-(4-*amino*-1 : 6-*dimethylpyrimidinium*-2-*amino*)-1 : 2-*dimethylquinolinium Salts and Related Compounds.*

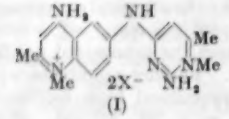
By (the late) F. H. S. CURD and Miss D. N. RICHARDSON.

[Reprint Order No. 6149.]

The preparation of analogues of "Antrycide" wherein a quaternised pyrimidine nucleus is linked through the 2-position to a quinolinium salt is described. The structure of the intermediate 4-amino-1 : 6-dimethylpyrimidinium iodides with a reactive group in the 2-position was established by hydrolysis to 1 : 6-dimethyluracil and that of 4-amino-2-chloro-1-methylpyrimidinium iodide by removal of the 2-chlorine atom to give 4-amino-1-methylpyrimidinium iodide.

IN the investigation of compounds related to "Antrycide" salts [4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium salts] (I), it was desirable to study the compounds wherein a quaternised pyrimidine nucleus was linked through the 2-position to the 6-position of a 4 : 6-diamino-1 : 2-dimethylquinolinium salt, *e.g.* (II; R = R'' = Me, R = NH_2, X = I; and R = Me, R' = NH_2, R'' = H, X = I). The unquaternised compound, 4-amino-6-(4-amino-6-methyl-2-pyrimidylamino)-2-methylquinoline (III), has been described (*J.*, 1953, 50) and the present communication describes the preparation of its quaternary derivatives and of related compounds.

Attempts were made to introduce two quaternary methyl groups directly into the base (III) by the action of methyl iodide and of methyl sulphate, but pure products were hard to obtain. So quaternary pyrimidine derivatives of type (IV; R = SMe or Cl, R' = Me) were prepared, having a reactive group in the 2-position.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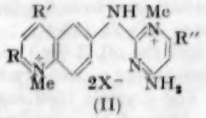
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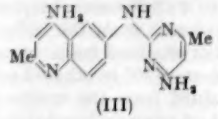
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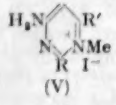
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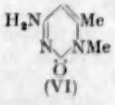
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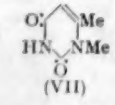
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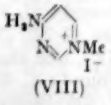

(VIII)

With methyl iodide in 2-ethoxyethanol under reflux, 4-amino-2-chloro-6-methylpyrimidine (IV; R = Cl, R' = Me) (Gabriel and Colman, *Ber.*, 1899, **32**, 2921) gave 4-amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (V; R = Cl, R' = Me). Careful crystallisation failed to show the presence of the 3 : 6-dimethyl isomer. The crude salt and the crystallised material were separately condensed with aniline, to give 4-amino-2-anilino-1 : 6-dimethylpyrimidinium iodide (V; R = NHPh, R' = Me) in yields comparable in both quality and quantity. With methyl iodide in boiling methanol, 4-amino-2-anilino-6-

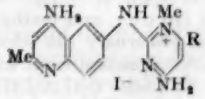
* Part II, *J.*, 1953, 59.

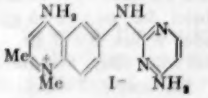
methylpyrimidine (IV; R = NHPh, R′ = Me) (Gabriel and Colman, *loc. cit.*) gave the same iodide (V; R = NHPh, R′ = Me). The structure of the chloro-compound (V; R = Cl, R′ = Me) was proved by a two-stage alkaline hydrolysis, first, to 4-amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI), and then to 1 : 6-dimethyluracil (VII), the constitution of which is well established (Behrend and Thurm, *Annalen*, 1902, **323**, 160; Behrend and Hesse, *ibid.*, 1903, **329**, 341).

The pyrimidinium salt (V; R = Cl, R′ = Me), with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride in hot aqueous solution, gave, after conversion of the product into the iodide, 4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium di-iodide (II; R = R″ = Me, R′ = NH_2, X = I). With 4 : 6-diamino-2-methylquinoline and 6-amino-1-methylquinolinium iodide, it gave 4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-2-methylquinoline iodide (IX; R = Me) and 6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1-methylquinolinium di-iodide (II; R = R′ = H, R″ = Me, X = I) respectively.

An alternative intermediate was the pyrimidine with a labile 2-methylthio-group. With methyl iodide in methanol under reflux, 4-amino-6-methyl-2-methylthiopyrimidine (IV; R = SMe, R′ = Me) (Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41) gave 4-amino-1 : 6-dimethyl-2-methylthiopyrimidinium iodide (V; R = SMe, R′ = Me), this structure being established by hydrolysis by acid or alkali to 4-amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI). Attempts to replace the methylthio-group of the product (V; R = SMe, R′ = Me) by an anilino-residue were unsuccessful. Replacement by a quinoline residue was therefore not attempted.

The diquaternary salt (II; R = Me, R′ = NH_2, R″ = H, X = I) was prepared by heating 4-amino-2-chloro-1-methylpyrimidinium iodide (V; R = Cl, R′ = H) with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide in aqueous acid. The pyrimidine derivative (V; R = Cl, R′ = H) was prepared by heating 4-amino-2-chloropyrimidine (IV; R = Cl, R′ = H) (Gabriel, *Ber.*, 1905, **38**, 1691) under reflux with methyl iodide in 2-ethoxyethanol and its structure proved by removal of the 2-chlorine atom to give 4-amino-1-methylpyrimidinium iodide (VIII) of proved constitution (see the following paper). The use of

(IX) 

 (X)

4 : 6-diamino-2-methylquinoline instead of 4 : 6-diamino-1 : 2-dimethylquinolinium iodide gave the monoquaternary salt (IX; R = H). An isomer of it, namely, (X), was similarly prepared from 4-amino-2-chloropyrimidine (IV; R = Cl, R′ = H) and 4 : 6-diamino-1 : 2-dimethylquinolinium iodide.

The quaternary pyrimidylaminoquinoline derivatives described above had a trypanocidal activity much lower than that of " Antrycide."

Experimental

4-Amino-2-chloro-1 : 6-dimethylpyrimidinium Iodide (V; R = Cl).—4-Amino-2-chloro-6-methylpyrimidine (Gabriel and Colman, *loc. cit.*) (28·5 g.), 2-ethoxyethanol (100 c.c.), and methyl iodide (27·2 c.c.) were heated under reflux for 6 hr. After cooling, the product was filtered off and washed with a small volume of 2-ethoxyethanol and with hot ethyl acetate. Thus prepared it had m. p. 198—200° (decomp.) and was pure enough for further work (yield, 32 g.). The *quaternary salt* was crystallised from hot water from which it separated as colourless prisms, m. p. 198—200° (decomp.) (Found : C, 25·05; H, 3·2; N, 14·4%; 1 mg. equiv. to 1·315 mg. of Ag halide. $C_6H_9N_3ClI$ requires C, 25·2; H, 3·2; N, 14·7%; 1 mg. equiv. to 1·28 mg. of Ag halide).

4-Amino-1 : 6-dimethyl-2-methylthiopyrimidinium Iodide (V; R = SMe).—4-Amino-6-methyl-2-methylthiopyrimidine (Hull *et al.*, *loc. cit.*) (7·75 g.), methyl iodide (6·2 c.c.), and methanol (100 c.c.) were heated under reflux for 15 hr. After cooling, the solid which had crystallised was filtered off and dried. Crystallisation from water gave the *quaternary salt* as needles, m. p. 258°

(decomp.) (Found: C, 28·3; H, 4·0; N, 14·65; I, 42·4. $C_7H_{12}N_3SI$ requires C, 28·3; H, 4·0; N, 14·1; I, 42·8%).

4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI).—4-Amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (1·0 g.) and N-sodium hydroxide (20 c.c.) were heated under reflux for 15 min. The *oxopyrimidine*, which separated on cooling, crystallised from water in colourless prisms, m. p. 340—342° (decomp.) (Found: C, 51·65; H, 6·2; N, 30·25. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%). The same compound was obtained by the action of boiling concentrated hydrochloric acid or of cold dilute alkali on 4-amino-1 : 6-dimethyl-2-methylthiopyrimidinium iodide.

Hydrolysis of 4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI).—4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (1·0 g.) and N-sodium hydroxide (20 c.c.) were heated under reflux for 5 hr. The solution was filtered and the filtrate acidified with 2N-hydrochloric acid. The acid solution was evaporated to dryness in a vacuum, and the residue extracted with boiling, dry alcohol. The residue, after evaporation of the alcohol, was sublimed in a high vacuum (bath-temp. 140—150°). The sublimate crystallised from alcohol had m. p. 220°, undepressed on admixture with 1 : 6-dimethyluracil.

4-Amino-2-anilino-1 : 6-dimethylpyrimidinium Iodide (V; R = NHPh).—(*a*) 4-Amino-2-anilino-6-methylpyrimidine (3·0 g.), ethanol (10 c.c.), and methyl iodide (4·5 c.c.) were heated under reflux for 4 hr. The white *salt* which separated on cooling crystallised from water as rhombs, m. p. 266° (decomp.) (Found: C, 41·55; H, 4·4; N, 16·0; I, 36·55. $C_{12}H_{13}N_4I$ requires C, 42·1; H, 4·4; N, 16·4; I, 37·1%).

Addition of sodium hydroxide solution to an aqueous solution precipitated the anhydro-base (*2-anilino-1 : 4-dihydro-4-imino-6-methylpyrimidine*) which crystallised from chlorobenzene as colourless cubes, m. p. 230° (Found, in material dried in a vacuum at 100°: C, 67·15; H, 6·5. $C_{12}H_{14}N_4$ requires C, 67·2; H, 6·5%).

(*b*) 4-Amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (2·85 g.), aniline (0·95 g.), water (20 c.c.), and concentrated hydrochloric acid (3 drops) were heated under reflux for 1 hr. The solid, which separated on cooling, was filtered off and dissolved in water, and the solution made alkaline with aqueous sodium hydroxide. The precipitated solid was filtered off and, after drying, crystallised from chlorobenzene: it had m. p. and mixed m. p. 230—232°. The crude starting material as described above gave similar results.

4-Amino-2-chloro-1-methylpyrimidinium Iodide (V; R = Cl, R′ = H).—4-Amino-2-chloropyrimidine (Gabriel, *loc. cit.*) (2·85 g.), 2-ethoxyethanol (10 c.c.), and methyl iodide (1·5 c.c.) were heated under reflux for 5 hr. After cooling, the *quaternary salt* which separated was collected, washed with ethyl acetate, and purified by crystallisation from water, then having m. p. 202—204° (decomp.) (Found: C, 22·2; H, 2·6; N, 15·0. $C_5H_7N_3ClI$ requires C, 22·1; H, 2·6; N, 15·4%).

4-Amino-1-methylpyrimidinium Iodide (VIII).—4-Amino-2-chloro-1-methylpyrimidinium iodide (1·0 g.), hydriodic acid (55%; 10 c.c.), and red phosphorus (2·0 g.) were heated on the steam-bath for 45 min. After dilution with water (20 c.c.) and filtration, the filtrate was evaporated to dryness in a vacuum. The residue had m. p. 202—204° after crystallisation from alcohol–ethyl acetate, undepressed in admixture with 4-amino-1-methylpyrimidinium iodide.

4-Amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium Di-iodide (II; R = R″ = Me, R′ = NH_2, X = I).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride (2·6 g.), 4-amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (2·8 g.), water (10 c.c.), and concentrated hydrochloric acid (1·0 c.c.) were heated under reflux for 1 hr. The solid which crystallised on cooling was dissolved in water and salted out with sodium iodide. The *quinolinium di-iodide* crystallised from water as flat prisms, m. p. 298—300° (decomp.) (Found: C, 33·9; H, 4·4; N, 14·35; I, 41·75. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·3; N, 14·0; I, 42·3%).

Similarly, from 4 : 6-diamino-2-methylquinoline, *4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-2-methylquinoline iodide* (IX), m. p. 254°, was obtained (Found: C, 41·35; H, 5·3; N, 18·05; I, 26·95. $C_{16}H_{19}N_6I,2·5H_2O$ requires C, 41·1; H, 5·1; N, 18·0; I, 27·2%). The use of 6-amino-1-methylquinolinium chloride gave *6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1-methylquinolinium di-iodide* (II; R = R′ = H, R″ = Me), m. p. 282° (decomp.) (Found: C, 34·0; H, 3·45; N, 12·05; I, 45·05. $C_{16}H_{19}N_5I_2,1·5H_2O$ requires C, 34·2; H, 3·9; N, 12·5; I, 45·2%).

Similar reactions of 4-amino-2-chloro-1-methylpyrimidinium iodide with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide and 4 : 6-diamino-2-methylquinoline gave *4-amino-6-(4-amino-1-methylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium di-iodide* (II; R = Me, R′ = NH_2, R″ =

H, X = I), m. p. 316—318° (decomp.) (Found: C, 33·0; H, 4·35; N, 14·9. $C_{16}H_{20}N_6I_2,H_2O$ requires C, 33·8; H, 3·9; N, 14·8%), and *4-amino-6-(4-amino-1-methylpyrimidinium-2-amino)-2-methylquinoline iodide hydriodide* (IX; R = H), m. p. >300° after crystallisation from water (Found: C, 31·3; H, 4·0; N, 14·4. $C_{15}H_{17}N_6I,HI$ requires C, 31·4; H, 3·8; N, 14·7%) respectively.

4-Amino-6-(4-amino-2-pyrimidylamino)-1 : 2-dimethylquinolinium Iodide Hydriodide (X).—4-Amino-2-chloropyrimidine (2·0 g.), 4 : 6-diamino-1 : 2-dimethylquinolinium iodide (4·85 g.), water (15 c.c.), and concentrated hydrochloric acid (1·0 c.c.) were heated under reflux for 1 hr. The *product* was filtered off and crystallised from water; it then had m. p. 340—342° (decomp.) (Found: C, 33·75; H, 3·2. $C_{15}H_{17}N_6I,HI$ requires C, 33·6; H, 3·4%).

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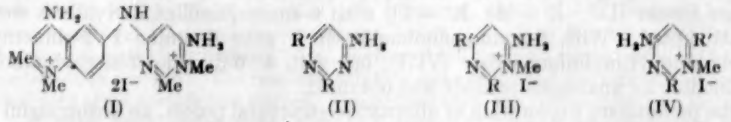
The Synthesis of Trypanocides. Part IV. The Attempted Preparation of 4-Amino-6-(6-amino-1 : 2-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium Di-iodide.*

By (the late) F. H. S. CURD and Miss D. N. RICHARDSON.

[Reprint Order No. 6150.]

The attempted preparation of the isomer of "Antrycide" in which the methyl group in the 6-position of the pyrimidine ring and the amino-group in the 2-position are interchanged, is described. The structure of the products of quaternisation of 6-amino-4-chloro-2-methylpyrimidine is established by degradation of 4-amino-6-chloro-1 : 2-dimethylpyrimidinium iodide, the major product, to 1 : 4-dihydro-1 : 2-dimethyl-4-oxopyrimidine which has been related to 1 : 6-dihydro-1-methyl-6-oxopyrimidine, synthesised by an unambiguous route. An account is also given of some exploratory work on alternative structural proofs.

FOR the preparation of the isomer (I) of "Antrycide" in which the methyl group in the 6-position of the pyrimidine ring and the amino-group in the 2-position are interchanged, the most direct method seemed to be reaction between a 6-amino-4-chloro-1 : 2-dimethylpyrimidinium salt, *e.g.* (III; R = Me, R′ = Cl), and a 4 : 6-diamino-1 : 2-dimethylquinolinium salt.



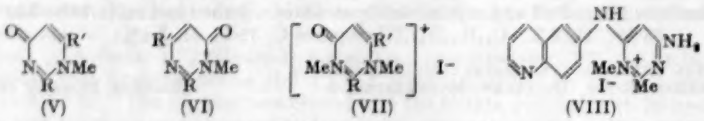
6-Amino-4-chloro-2-methylpyrimidine (II; R = Me, R′ = Cl) (Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383), with methyl iodide in 2-ethoxyethanol under reflux, gave a mixture of two isomeric quaternary iodides (III and IV; R = Me, R′ = Cl), the second being by far the more abundant constituent.† These exchanged chlorine for an aniline residue, giving the iodides (III and IV; R = Me, R′ = NHPh), both of which were also obtained by the action of methyl iodide on 6-amino-4-anilino-2-methylpyrimidine (II; R = Me, R′ = NHPh). The proof of the constitution of these two pairs of quaternary derivatives is the main subject of this paper.

The first stage in this proof was the reduction of the chloro-compound (IV; R = Me, R′ = Cl) by zinc dust to 4-amino-1 : 2-dimethylpyrimidinium iodide (IV; R = Me, R′ = H), which was also obtained from 4-amino-2-methylpyrimidine (Gabriel, *Ber.*, 1904,

* Part III, preceding paper.

† Preparation of these quaternary derivatives is described in B.P. 634,417.

37, 3638) and methyl iodide and on alkaline hydrolysis gave 1 : 4-dihydro-1 : 2-dimethyl-4-oxopyrimidine (V; R = Me, R′ = H). The isomeric 6-oxo-compound (VI; R = Me, R′ = H) was obtained from 4-hydroxy-2-methylpyrimidine (Gabriel, *loc. cit.*; Cheruliez and Stavritch, *Helv. Chim. Acta*, 1922, **5**, 267) by methylation. That these products (V and VI; R = Me, R′ = H) were isomers of the type postulated was proved when with methyl iodide under pressure they gave the same 1 : 4-dihydro-1 : 2 : 3-trimethyl-4-oxopyrimidinium iodide (VII; R = Me, R′ = H).



The further work on the proof of the structure was carried out on the compound (VI; R = Me, R′ = H) since this was the more readily available isomer. An attempt at its unambiguous synthesis was unsuccessful. Cheruliez and Stavritch (*loc. cit.*) had prepared 4-hydroxy-2-methylpyrimidine by decarboxylation of 6-hydroxy-2-methylpyrimidine-4-carboxylic acid, which was obtained by the ring closure of the Schiff's base from acetaldehyde and the ω-amide of aspartic acid. However, the ring closure of the Schiff's base from acetaldehyde and the methylamide of aspartic acid could not be accomplished. Attention was therefore turned to relating the compound to a pyrimidine or uracil derivative of proved structure, in particular to elimination of the 2-methyl group. The 2-methyl group in (VI; R = Me, R′ = H) was remarkably stable to oxidising agents; it was not attacked by fuming nitric acid or neutral potassium permanganate. Attempts at side-chain bromination failed to give recognisable products capable of hydrolysis to known compounds. However, with benzaldehyde and zinc chloride, the compound gave the 2-styryl derivative (VI; R = CH:CHPh, R′ = H) (cf. Kondo and Yanoi, *J. Pharm. Soc. Japan*, 1937, **57**, 747; 1938, **58**, 397), which on oxidation with potassium permanganate in dry acetone followed by sublimation of the product in a high vacuum gave 1 : 6-dihydro-1-methyl-6-oxopyrimidine (VI; R = R′ = H) the structure of which has been proved by Brown, Hoerger, and Mason (*J.*, 1955, 213). Methylation of 4-hydroxypyrimidine (Wheeler, *Amer. Chem. J.*, 1909, **42**, 301) and desulphurisation of 1 : 6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine with Raney nickel also gave this substance. Thus the constitutions of the compounds (VI; R = Me, R′ = H) and (IV; R = Me, R′ = Cl) were established.

Owing to the very small proportion of the isomer (III; R = Me, R′ = Cl) in the products of quaternisation of 6-amino-4-chloro-2-methylpyrimidine, the synthesis of the " Antrycide " analogue (I) was not attempted from this intermediate. Some reactions of the other isomer (IV; R = Me, R′ = Cl) with 6-aminoquinoline derivatives were, however, attempted. With 6-aminoquinoline itself it gave 4-amino-1 : 2-dimethyl-6 : 6′-quinolylaminopyrimidinium iodide (VIII), but with 4 : 6-diamino-2-methylquinoline and its methiodide no analogous product was obtained.

In the preliminary exploration of alternative structural proofs, an unsuccessful attempt was made to obtain 1 : 6-dihydro-1-methyl-6-oxopyrimidine by removal of the 4-methyl group from the 1 : 4-dimethyl compound (VI; R = H, R′ = Me). This was obtained either by methylation of 6-hydroxy-4-methylpyrimidine (Gabriel and Colman, *Ber.*, 1899, **32**, 2921) or by the treatment of 1 : 6-dihydro-1 : 4-dimethyl-2-methylthio-6-oxopyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 106) with Raney nickel. Its structure was confirmed by heating it with methyl iodide under pressure; it gave 1 : 4-dihydro-1 : 3 : 6-trimethyl-4-oxopyrimidinium iodide (VII; R = H, R′ = Me) identical with that obtained by a similar process from the isomeric 1 : 4-dihydro-1 : 6-dimethyl-4-oxopyrimidine (V; R = H, R′ = Me), which was synthesised in the following way. Reduction of 4-amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (IV; R = Cl, R′ = Me) (previous paper) with hydriodic acid gave 4-amino-1 : 6-dimethylpyrimidinium iodide (IV; R = H, R′ = Me), also obtained either by quaternisation of 4-amino-6-methylpyrimidine (Gabriel and Colman, *loc. cit.*) or by the action of Raney nickel on 4-amino-1 : 2-dihydro-1 : 6-dimethyl-2-thiopyrimidine (the corresponding 2-methylthio-compound could not be used). Alkaline

hydrolysis of the product (IV; R = H, R′ = Me) gave 1 : 4-dihydro-1 : 6-dimethyl-4-oxopyrimidine (V; R = H, R′ = Me). The 4-methyl group in 1 : 6-dihydro-1 : 4-dimethyl-6-oxopyrimidine was unattacked by oxidising agents such as nitric acid, potassium permanganate, and selenium dioxide, and no styryl compound could be obtained.

When work on the orientation of these pyrimidine derivatives was first undertaken, it was planned to convert 1 : 4-dihydro-1 : 2-dimethyl-4-oxopyrimidine (V; R = Me, R′ = H) into 1 : 4-dihydro-1-methyl-4-oxopyrimidine (V; R = R′ = H), an authentic sample of which would be prepared from 1 : 4-dihydro-1 : 6-dimethyl-4-oxopyrimidine (V; R = H, R′ = Me). The low yields of (V; R = Me, R′ = H and R = H, R′ = Me) made this impracticable, but experiments were carried out on the preparation of (V; R = R′ = H). 4-Aminopyrimidine (Büttner, *Ber.*, 1903, **36**, 2227; Wheeler and Johnson, *J. Biol. Chem.*, 1907, **3**, 183) and methyl iodide in 2-ethoxyethanol under reflux gave 4-amino-1-methylpyrimidinium iodide (IV; R = R′ = H). Subsequent alkaline hydrolysis gave 1 : 4-dihydro-1-methyl-4-oxopyrimidine (V; R = R′ = H), and the relation between this compound and the isomer (VI; R = R′ = H) previously described was demonstrated by conversion of both into 1 : 4-dihydro-1 : 3-dimethyl-4-oxopyrimidinium iodide (VII; R = R′ = H).

Experimental

4-Amino-6-chloro-1 : 2-dimethylpyrimidinium Iodide (IV; R = Me, R′ = Cl).—6-Amino-4-chloro-2-methylpyrimidine (Baddiley *et al.*, *loc. cit.*) (25·8 g.), 2-ethoxyethanol (100 c.c.), and methyl iodide (27·2 c.c.) were heated on the steam-bath for 6 hr. After filtration, the *pyrimidinium iodide* was washed with boiling ethyl acetate and crystallised from water as flat prisms, m. p. 244—246° (decomp.) (10·1 g.) (Found: C, 25·1; H, 3·0; N, 14·35%; 1 mg. equiv. to 1·31 mg. of Ag halide. $C_6H_9N_3ClI$ requires C, 25·2; H, 3·2; N, 14·7%; 1 mg. equiv. to 1·28 mg. of Ag halide).

6-Amino-4-chloro-1 : 2-dimethylpyrimidinium Iodide (III; R = Me, R′ = Cl).—The 2-ethoxyethanol solution remaining after filtration of the iodide (IV; R = Me, R′ = Cl) (see above) was evaporated in a vacuum and the isomeric *pyrimidinium iodide* purified by crystallisation from water: it had m. p. 232—234° (decomp.) (Found: C, 24·9; H, 3·05%; 1 mg. equiv. to 1·32 mg. of Ag halide).

6-Amino-4-anilino-2-methylpyrimidine (II; R = Me, R′ = NHPh).—6-Amino-4-chloro-2-methylpyrimidine (2·4 g.), aniline (1·5 c.c.), water (10 c.c.), and concentrated hydrochloric acid (0·1 c.c.) were heated under reflux for 1 hr. The cooled solution was diluted with water and made alkaline with ammonia. The precipitated solid was filtered off and dissolved in aqueous-alcoholic ammonia. The crude *pyrimidine* was precipitated by dilution with water and crystallised from chlorobenzene as plates, m. p. 190—191° (Found, in material dried in a vacuum at 100°: C, 65·75; H, 5·8; N, 27·75. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%).

4-Amino-6-anilino-1 : 2-dimethylpyrimidinium Iodide (IV; R = Me, R′ = NHPh).—(*a*) 6-Amino-4-anilino-2-methylpyrimidine (7·5 g.), methanol (50 c.c.) and methyl iodide (12 c.c.) were heated under reflux for 4 hr. The resulting solution was evaporated to dryness, and the residue was treated with ethyl acetate and filtered. Crystallisation of the residue first from alcohol–ethyl acetate and then from water gave *4-amino-6-anilino-1 : 2-dimethylpyrimidinium iodide* as prisms, m. p. 274—276° (Found: C, 41·75; H, 4·35; N, 16·75; I, 36·8. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4; I, 37·1%).

(*b*) 4-Amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (2·9 g.), aniline (1·8 g.), and water (10 c.c.) were heated under reflux for 2 hr. The solid which separated crystallised from water and had m. p. and mixed m. p. 274—276°.

6-Amino-4-anilino-1 : 2-dimethylpyrimidinium Iodide (III; R = Me, R′ = NHPh).—(*a*) The alcohol–ethyl acetate liquors [see (*a*) above] were evaporated to dryness; the *pyrimidinium iodide* crystallised from water as colourless prisms, m. p. 228—230° (Found: C, 41·85; H, 4·6; N, 16·15; I, 36·75%).

(*b*) 6-Amino-4-chloro-1 : 2-dimethylpyrimidinium iodide (0·85 g.), aniline (0·5 c.c.), and water (5 c.c.), as above, gave the preceding compound, m. p. and mixed m. p. 230—232° (from water).

4-Amino-1 : 2-dimethylpyrimidinium Iodide (IV; R = Me, R′ = H).—(*a*) 4-Amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (2·0 g.), zinc dust (20 g.), and water (200 c.c.) were boiled together for 1·5 hr. The suspension was filtered, and the filtrate evaporated to dryness in a

vacuum. *4-Amino-1 : 2-dimethylpyrimidinium iodide* thus obtained had m. p. 246—248° after crystallisation from alcohol (Found : C, 28·7; H, 3·85; N, 16·85; I, 50·5. $C_6H_{10}N_2I$ requires C, 28·7; H, 4·0; N, 16·75; I, 50·6%).

(*b*) 4-Amino-2-methylpyrimidine (Gabriel, *loc. cit.*) (8·2 g.), 2-ethoxyethanol (15 c.c.), and methyl iodide (10·5 c.c.), as above, gave the same salt (11·9 g.), m. p. and mixed m. p. 246—248° (from 75% aqueous alcohol; prisms).

1 : 4-*Dihydro*-1 : 2-*dimethyl*-4-*oxopyrimidine* (V; R = Me, R′ = H).—4-Amino-1 : 2-dimethylpyrimidinium iodide (2·5 g.), potassium hydroxide (0·56 g.), and water (20 c.c.) were heated under reflux for 1 hr. The solution was evaporated to dryness in a vacuum and the residue extracted with dry acetone. Evaporation of the acetone solution gave 1 : 4-dihydro-1 : 2-dimethyl-4-oxopyrimidine. It formed a *picrate*, m. p. 178—180° (from 2-ethoxyethanol) (Found : C, 41·1; H, 3·6; N, 19·55. $C_6H_8ON_2,C_6H_3O_7N_3$ requires C, 40·8; H, 3·1; N, 19·8%).

1 : 6-*Dihydro*-1 : 2-*dimethyl*-6-*oxopyrimidine* (VI; R = Me, R′ = H).—4-Hydroxy-2-methylpyrimidine (Gabriel, *loc. cit.*; Cheruliez and Stavritch, *loc. cit.*) (3·3 g.) was dissolved in a solution of potassium hydroxide (1·68 g.) in alcohol (25 c.c.). Methyl iodide (2·1 c.c.) was added and the mixture warmed on the steam-bath until the solution no longer gave an alkaline reaction on Brilliant-yellow paper. After cooling, the solution was filtered, the filtrate evaporated to dryness in a vacuum, and the residue sublimed in a high vacuum. 1 : 6-*Dihydro*-1 : 2-*dimethyl*-6-*oxopyrimidine* was a hygroscopic white solid (Found : C, 57·9; H, 6·4. $C_6H_8ON_2$ requires C, 58·1; H, 6·5%). Addition of concentrated nitric acid to an acetone solution precipitated the *nitrate*, m. p. 162° (decomp.) (from methanol) (Found : C, 38·3; H, 4·15; N, 22·2 $C_6H_8ON_2,HNO_3$ requires C, 38·5; H, 4·8; N, 22·4%). Similarly, hydrochloric acid gave the *hydrochloride*, plates, m. p. 250° (decomp.) (from methanol) (Found : C, 44·25; H, 5·45; N, 16·9. $C_6H_8ON_2,HCl$ requires C, 44·9; H, 5·6; N, 17·4%), and methanolic picric acid the *picrate*, parallelepipeds, m. p. 172° (from 2-ethoxyethanol) (Found : C, 40·55; H, 3·15; N, 19·65. $C_6H_8ON_2,C_6H_3O_7N_3$ requires C, 40·8; H, 3·1; N, 19·8%).

1 : 4-*Dihydro*-1 : 2 : 3-*trimethyl*-4-*oxopyrimidinium Iodide* (VII; R = Me, R′ = H).—1 : 6-Dihydro-1 : 2-dimethyl-6-oxopyrimidine (2·4 g.) and methyl iodide (1·24 c.c.) were heated in a sealed tube at 100° for 6 hr. The *pyrimidinium iodide* crystallised from alcohol as plates, m. p. 224° (decomp.) (Found : C, 31·95; H, 4·45; N, 10·75. $C_7H_{11}ON_2I$ requires C, 31·6; H, 4·1; N, 10·5%). The same compound was obtained from 1 : 4-dihydro-1 : 2-dimethyl-4-oxopyrimidine and methyl iodide.

1 : 6-*Dihydro*-1-*methyl*-6-*oxo*-2-*styrylpyrimidine* (VI; R = CH:CHPh, R′ = H).—1 : 6-Dihydro-1 : 2-dimethyl-6-oxopyrimidine (3·72 g.), benzaldehyde (3·6 c.c.), and anhydrous zinc chloride (0·8 g.) were heated together in a sealed tube for 3 hr. at 110—120°. The *styryl compound*, which separated on cooling, had m. p. 136° after crystallisation first from benzene–light petroleum (b. p. 60—80°), then from alcohol (yield, 1·25 g.) (Found : C, 73·1; H, 5·35; N, 13·2. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·0%).

1 : 6-*Dihydro*-1-*methyl*-6-*oxopyrimidine* (VI; R = R′ = H).—(*a*) 1 : 6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine (0·8 g.), methanol (25 c.c.), and Raney nickel (10 g.) were stirred under reflux for 2 hr. The nickel was removed and the filtrate evaporated to dryness in a vacuum. 1 : 6-Dihydro-1-methyl-6-oxopyrimidine thus obtained was converted into the *picrate* which crystallised first from 2-ethoxyethanol and then from water as rectangular prisms, m. p. 176—178° (Found : C, 38·7; H, 2·75; N, 20·5. $C_5H_6ON_2,C_6H_3O_7N_3$ requires C, 38·3; H, 2·6; N, 20·65%).

(*b*) 1 : 6-Dihydro-1-methyl-6-oxo-2-stryrylpyrimidine (2·7 g.) was dissolved in acetone (150 c.c., dried over P_2O_5), and excess of potassium permanganate (8·3 g.) added. The mixture was filtered, the residue extracted with boiling water (200 c.c.), and the extract neutralised with hydrochloric acid and evaporated to dryness in a vacuum. The residue was sublimed in a vacuum and the sublimate converted into the picrate, m. p. and mixed m. p. 176—178° (from water).

(*c*) 4-Hydroxypyrimidine (Wheeler, *loc. cit.*) (2·88 g.) was dissolved in a solution of potassium hydroxide (1·68 g.) in alcohol (25 c.c.) and heated under reflux with methyl iodide (2·06 c.c.) until the mixture was no longer alkaline. The precipitated solid was filtered off, the filtrate evaporated to dryness in a vacuum, and the residue sublimed in a high vacuum. The sublimate was 1 : 6-*dihydro*-1-*methyl*-6-*oxopyrimidine* (Found : C, 54·9; H, 5·4. $C_5H_6ON_2$ requires C, 54·5; H, 5·4%). It formed a picrate, m. p. and mixed m. p. 176—178° (from 2-ethoxyethanol).

4-*Amino*-1 : 2-*dimethyl*-6-6′-*quinolylaminopyrimidinium Iodide* (VIII).—4-Amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (2·85 g.), 6-aminoquinoline (2·88 g.), and water (10 c.c.) were heated together under reflux for 3 hr. The *pyrimidinium iodide*, which separated on cooling,

was collected and dissolved in water. The aqueous solution was filtered from a little insoluble material and the filtrate salted with sodium iodide. The *iodide* crystallised from 50% ethanol as flat prisms, m. p. 268—270° (Found: C, 43·65; H, 4·4; I, 31·1. $C_{15}H_{16}N_8I,H_2O$ requires C, 43·8; H, 4·4; I, 30·9%).

1 : 6-*Dihydro*-1 : 4-*dimethyl*-6-*oxopyrimidine* (VI; R = H, R′ = Me).—(*a*) 6-Hydroxy-4-methylpyrimidine hydriodide (Gabriel and Colman, *loc. cit.*) (14·28 g.), potassium hydroxide (6·72 g.), alcohol (50 c.c.), and methyl iodide (4·13 c.c.) were heated under reflux for 2 hr. After cooling, the mixture was filtered and the filtrate evaporated to dryness in a vacuum. The residue was sublimed in a high vacuum (bath-temp. 100°). The sublimate of 1 : 6-dihydro-1 : 4-dimethyl-6-oxopyrimidine was hygroscopic. It formed a *picrate*, m. p. 188—190° (from 2-ethoxyethanol) (Found: C, 40·55; H, 3·05; N, 19·6. $C_6H_8ON_2,C_6H_3O_7N_3$ requires C, 40·8; H, 3·1; N, 19·8%).

(*b*) 1 : 6-Dihydro-1 : 4-dimethyl-2-methylthio-6-oxopyrimidine (Wheeler and McFarland, *loc. cit.*) (1·0 g.) was heated under reflux with Raney nickel (10·0 g.) in methanol (100 c.c.) for 2 hr. The nickel was removed and the filtrate evaporated to dryness in a vacuum. The residue formed a picrate, yellow prisms (from 2-ethoxyethanol), m. p. and mixed m. p. 188—190°.

4-*Amino*-1 : 2-*dihydro*-1 : 6-*dimethyl*-2-*thiopyrimidine*.—Sodium (0·92 g.) was dissolved in alcohol (50 c.c.) and hydrogen sulphide passed in until the gain in weight was 1·3 g. This solution was added to a suspension of 4-amino-1 : 6-dimethyl-2-methylthiopyrimidinium iodide (previous paper) (5·66 g.) in alcohol (50 c.c.), and the mixture heated under reflux for 1 hr., hydrogen sulphide being passed through the solution. After cooling, the *dihydropyrimidine* was collected and crystallised from water: it had m. p. 322° (decomp.) (yield, 2·5 g.) (Found: C, 45·6; H, 6·0; N, 26·65; S, 21·15. $C_6H_9N_3S$ requires C, 46·5; H, 5·8; N, 27·1; S, 20·6%).

4-*Amino*-1 : 6-*dimethylpyrimidinium Iodide* (IV; R = H, R′ = Me).—(*a*) 4-Amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (2·0 g.) and hydriodic acid (25 c.c.; *d* 1·7) were warmed together on the steam-bath for 0·25 hr. After dilution with water (25 c.c.) the mixture was neutralised with potassium carbonate. The *pyrimidinium iodide* was collected, washed with acetone, and purified by crystallisation from alcohol; it formed prisms, m. p. 262—264° (Found: C, 28·65; H, 3·9; N, 16·6. $C_6H_{10}N_3I$ requires C, 28·7; H, 4·0; N, 16·6%).

(*b*) 4-Amino-6-methylpyrimidine (Gabriel and Colman, *loc. cit.*) (11·0 g.), methyl iodide (14 c.c.), and 2-ethoxyethanol (25 c.c.) were heated under reflux on the steam-bath for 2·5 hr. The product, crystallised from 75% aqueous alcohol (70 c.c.), had m. p. and mixed m. p. 262—264° (yield, 15·7 g.).

(*c*) 4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-thiopyrimidine (2·1 g.) was stirred under reflux with Raney nickel (20 g.) in methanol (100 c.c.) for 3 hr. After filtration, the solution was made acid with hydriodic acid and evaporated to small bulk. The material which crystallised had m. p. and mixed m. p. 260—262°.

1 : 4-*Dihydro*-1 : 6-*dimethyl*-4-*oxopyrimidine* (V; R = H, R′ = Me).—4-Amino-1 : 6-dimethylpyrimidinium iodide (2·5 g.), potassium hydroxide (0·56 g.), and water (20 c.c.) were boiled together for 1 hr. The solution was evaporated to dryness in a vacuum and the residue extracted with dry acetone. The crude material remaining after evaporation of the acetone formed a *picrate*, m. p. 174—176° (from 2-ethoxyethanol) (Found: C, 41·25; H, 3·2; N, 19·75. $C_6H_8ON_2,C_6H_3O_7N_3$ requires C, 40·8; H, 3·1; N, 19·8%).

1 : 4-*Dihydro*-1 : 3 : 6-*trimethyl*-4-*oxopyrimidinium Iodide* (VII; R = H, R′ = Me).—1 : 6-Dihydro-1 : 4-dimethyl-6-oxopyrimidine (2·4 g.) and methyl iodide (2·0 c.c.) were heated together in a sealed tube at 100° for 6 hr. The *pyrimidinium iodide* crystallised from alcohol as plates, m. p. 268—270° (Found: C, 31·95; H, 4·45; N, 10·05; I, 48·25. $C_7H_{11}ON_2I$ requires C, 32·1; H, 4·25; N, 10·5; I, 47·7%). The same compound was obtained from 1 : 4-dihydro-1 : 6-dimethyl-4-oxopyrimidine and methyl iodide under pressure for 15 hr. at 100°.

4-*Amino*-1-*methylpyrimidinium Iodide* (IV; R = R′ = H).—4-Aminopyrimidine (Büttner, also Wheeler and Johnson, *locc. cit.*) (2·15 g.), 2-ethoxyethanol (10 c.c.), and methyl iodide (5 c.c.) were heated under reflux for 5 hr. The *pyrimidinium iodide* which separated (4·2 g.) crystallised from alcohol–ethyl acetate as prisms, m. p. 204—206° (Found: C, 25·9; H, 3·5; I, 53·1. $C_5H_8N_3I$ requires C, 25·3; H, 3·4; I, 53·6%).

1 : 4-*Dihydro*-1-*methyl*-4-*oxopyrimidine* (V; R = R′ = H).—4-Amino-1-methylpyrimidinium iodide (2·37 g.), potassium hydroxide (0·56 g.), and water (20 c.c.) were heated under reflux for 1 hr. The solution was evaporated to dryness in a vacuum and the residue extracted with hot acetone. The crude product remaining after evaporation of the solvent formed a *picrate*, m. p. 164—166° (from 2-ethoxyethanol) (Found: C, 38·25; H, 2·9; N, 20·15. $C_5H_6ON_2,C_6H_3O_7N_3$ requires C, 38·3; H, 2·6; N, 20·65%).

1 : 4-*Dihydro*-1 : 3-*dimethyl*-4-*oxopyrimidinium Iodide* (VII; R = R′ = H).—1 : 6-Dihydro-1-methyl-6-oxopyrimidine (0·7 g.) and methyl iodide (0·5 c.c.) were heated in a sealed tube for 6 hr. at 100°. The *pyrimidinium iodide* crystallised from alcohol as flat needles, m. p. 204—206° (Found : C, 29·0; H, 4·0; N, 11·1; I, 50·6. $C_6H_9ON_2I$ requires C, 28·5; H, 3·1; N, 11·1; I, 50·4%). The same compound was obtained from 1 : 4-dihydro-1-methyl-4-oxopyrimidine and methyl iodide.

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The Synthesis of Trypanocides. Part V. A Rearrangement of Some 6-Amino-1-methylpyrimidinium Salts, and the Synthesis of 4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)-quinolinium Di-iodide.*

By H. C. CARRINGTON, (the late) F. H. S. CURD, and Miss D. N. RICHARDSON.

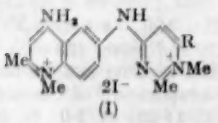
[Reprint Order No. 6151.]

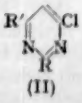
6-Amino-1-methylpyrimidinium salts which may carry hydrocarbon substituents in position 2 and arylamino-groups in position 4 are converted under alkaline conditions into the corresponding 6-methylaminopyrimidines.

4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)quinolinium di-iodide (I; R = NHMe) was prepared by the action of methylamine on the corresponding compound with a 6-methylthio-group in the pyrimidine nucleus.

A SECOND method (cf. Part IV *) investigated for the preparation of the isomer (I; R = NH_2) of " Antrycide " was the preparation of a compound (I; R = SMe or Cl) in which R could be replaced by an amino-group on treatment with ammonia. Preliminary work was carried out on the corresponding anilinopyrimidines and this paper is chiefly concerned with the preparation and reactions of these simple compounds.

By treatment of 6-chloro-2-methyl-4-methylthiopyrimidine (II; R = Me, R′ = SMe) with methyl sulphate in nitrobenzene, and isolation of the product as the iodide, a mixture


(I)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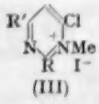
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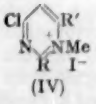
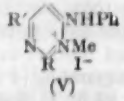

(IV)

of 6-chloro-1 : 2-dimethyl-4- (III; R = Me, R′ = SMe) and 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me, R′ = SMe) was obtained. These compounds were unstable, but with aniline gave the anilino-derivatives (V and VI; R = Me, R′ = SMe). The orientation of these pairs of quaternary salts was established by treating 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me,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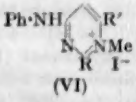
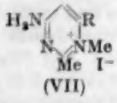

(VI)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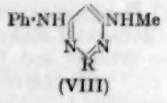
(VIII)

R′ = SMe) with aqueous ammonia, 4-amino-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (VII; R = SMe) being obtained, identical with that obtained by the action of sodium methyl sulphide on 4-amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (VII; R = Cl) the constitution of which was established as reported in the preceding paper.

Quaternisation of 4-anilino-6-chloro-2-methylpyrimidine (II; R = Me, R′ = NHPh)

* Part IV, preceding paper.

gave a single quaternary salt which proved to be 4-anilino-6-chloro-1 : 2-dimethylpyrimidinium iodide (VI; R = Me, R′ = Cl) since with sodium methyl sulphide it gave 4-anilino-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (VI; R = Me, R′ = SMe).

The action of liquid or alcoholic ammonia on the compounds (VI; R = Me, R′ = Cl; and R = Me, R′ = SMe) was then examined. The product, crystallised from dilute hydriodic acid, was not the expected iodide (VI; R = Me, R′ = NH_2; preceding paper) but an isomer. Titration showed that it was not a quaternary salt but the hydriodide of a weaker base, namely, 4-anilino-2-methyl-6-methylaminopyrimidine (VIII; R = Me), an authentic sample of which was prepared from 4-anilino-6-chloro-2-methylpyrimidine (II; R = Me, R′ = NHPh) and alcoholic methylamine.

In view of this unexpected transformation, the behaviour of 6-amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (VI; R = Me, R′ = NH_2) under alkaline conditions was investigated. Conversion into the base (VIII; R = Me) took place on treatment with alcoholic ammonia, aqueous sodium carbonate solution, or piperidine, but not with pyridine. It thus appears that in the reaction between the iodides (VI; R = Me, R′ = SMe; and R = Me, R′ = Cl) with ammonia a normal replacement first takes place and is followed by rearrangement of the quaternary compound. Similar rearrangements take place in analogous pyrimidines unsubstituted in the 2-position or with a 2-phenyl group, *i.e.*, in (VI; R = H, R′ = Cl, and R = Ph, R′ = Cl).

The rearrangement of the system ·NR·C(NH_2):· to ·N:C(NHR)· by alkali has been demonstrated in rings other than the pyrimidine. For instance, Dimroth (*Annalen*, 1909, **364**, 183) describes the rearrangement of 5-amino-1-phenyl-1 : 2 : 3-triazoles to 2-anilinotriazoles. More recently the rearrangement of 5-amino-1-aryl-1 : 2 : 3 : 4-tetrazoles to 5-anilino-1 : 2 : 3 : 4-tetrazoles has been demonstrated (Garbrecht and Herbst, *J. Org. Chem.*, 1953, **18**, 1269, 1283). In this series, however, 5-alkylaminotetrazoles rearrange in the reverse way to 5-amino-1-methyl-1 : 2 : 3 : 4-tetrazoles. Work on the metabolite of " Paludrine " has given examples of a somewhat similar change in the dihydrotriazines (Carrington, Crowther, and Stacey, *J.*, 1954, 1017) and the conversion of 5-amino-2-mercaptothiazoles by alkali into 2 : 4-dithiohydantoins (Cook, Heilbron, and Levy, *J.*, 1947, 1598) is a similar case in which hetero-atoms other than nitrogen are involved.

This pyrimidine transformation would almost certainly preclude the preparation of a compound (I; R = NH_2) by the reaction of the di-iodide (I; R = SMe or Cl) with ammonia. However, by treating the salts (VI; R = Me, R′ = Cl; and R = Me, R′ = SMe) with alcoholic methylamine the consequences of the rearrangement were avoided and the quaternary 4-anilino-1 : 2-dimethyl-6-methylaminopyrimidinium iodide (VI; R = Me, R′ = NHMe) was obtained.

A similar synthesis was therefore carried out with the corresponding pyrimidylaminoquinoline. 4-Chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide, with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide in hot water, gave the di-iodide (I; R = SMe), which with methanolic methylamine was converted into 4-amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)quinolinium di-iodide (I; R = NHMe).

Experimental

6-Chloro-2-methyl-4-methylthiopyrimidine (II; R = Me, R′ = SMe).—4-Chloro-6-hydroxy-2-methylpyrimidine (Basford, Curd, and Rose, *J.*, 1946, 713) (33·6 g.) and alcoholic sodium hydrogen sulphide [200 c.c.; prepared by dissolving sodium (9·6 g.) in alcohol (200 c.c.) and passing in hydrogen sulphide until gain in weight was 13·2 g.] were heated in an autoclave at 100° for 1 hr. The contents of the autoclave were diluted with water, treated with carbon, and filtered. Acidification with acetic acid precipitated 6-hydroxy-2-methyl-4-thiopyrimidine which was used without further purification. 6-Hydroxy-2-methyl-4-thiopyrimidine (25 g.) was suspended in a solution of sodium (3·68 g.) in methanol (75 c.c.), methyl iodide (16 c.c.) was added, and the mixture was heated under reflux for 1 hr. *6-Hydroxy-2-methyl-4-methylthiopyrimidine* separated on cooling and crystallised from alcohol as prisms, m. p. 222—224° (Found: C, 45·95; H, 4·85; N, 18·6. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1; N, 17·9%). 6-Hydroxy-2-methyl-4-methylthiopyrimidine (31·4 g.) and phosphoryl chloride (100 c.c.) were heated under reflux for 1 hr. The excess of phosphoryl chloride was evaporated under reduced

pressure, and the residue was poured on ice and made alkaline with ammonia. The crude product was extracted with ether, and, after drying and evaporation of the ether, the residue of *6-chloro-2-methyl-4-methylthiopyrimidine* was distilled in a vacuum; it had b. p. 126—128°/19 mm. (yield, 25·35 g.) (Found, in material dried in a vacuum at room temperature: C, 40·75; H, 4·35; N, 16·5. $C_6H_7N_2SCl$ requires C, 41·2; H, 4·0; N, 16·0%).

6-Chloro-1 : 2-*dimethyl*-4-*methylthiopyrimidinium Iodide* (III; R = Me, R′ = SMe).—6-Chloro-2-methyl-4-methylthiopyrimidine (25·35 g.) was dissolved in nitrobenzene (120 c.c.) at 90—95°. Methyl sulphate (72 c.c.) was added and the mixture was stirred at 90—95° for 1 hr. After cooling, the solution was extracted with water, and the aqueous extract was treated with excess of sodium iodide. The precipitated pyrimidinium iodide was collected, washed with acetone, and dried in a vacuum. The product was not sufficiently stable to be crystallised for analysis. The aqueous liquors gradually deposited the isomer, 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me, R′ = SMe).

4-*Amino*-6-*methylthio*-1 : 2-*dimethylpyrimidinium Iodide* (VII; R = SMe).—(*a*) 4-Amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (2·85 g.) was dissolved in water (20 c.c.), and alcoholic 2M-sodium methyl sulphide (5 c.c.) was added. Immediate reaction took place. Methanethiol was passed through the warmed solution for 15 min. and, after cooling, the *pyrimidinium iodide* was collected and crystallised from water as prisms, m. p. 260° (decomp.) (Found: C, 28·05; H, 3·95; N, 13·55. $C_7H_{13}N_2SI$ requires C, 28·3; H, 4·0; N, 14·1%).

(*b*) 4-Chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (1·5 g.) was stirred with aqueous ammonia (5 c.c.; *d* 0·88). The crude product was filtered off and crystallised from water; it had m. p. and mixed m. p. 260° (decomp.).

4-*Anilino*-6-*chloro*-1 : 2-*dimethylpyrimidinium Iodide* (VI; R = Me, R′ = Cl).—4-Anilino-6-chloro-2-methylpyrimidine (Basford, Curd, and Rose, *loc. cit.*) (5·5 g.) was dissolved in nitrobenzene (50 c.c.) at 60°. Methyl sulphate (6·5 c.c.) was added and the temperature was raised to 90—95° for 4·5 hr. The crude methosulphate which crystallised on cooling was collected and dissolved in water. Addition of sodium iodide to the aqueous solution precipitated the *pyrimidinium iodide*, flat needles, m. p. 212° (decomp.) (from water) (Found: C, 40·0; H, 3·8; N, 11·5. $C_{12}H_{13}N_3ClI$ requires C, 39·8; H, 3·6; N, 11·6%).

6-*Anilino*-1 : 2-*dimethyl*-4-*methylthiopyrimidinium Iodide* (V; R = Me, R′ = SMe).—6-Chloro-1 : 2-dimethyl-4-methylthiopyrimidinium iodide (1·58 g.), aniline (0·46 g.), and water (10 c.c.) were heated under reflux for 1 hr. The *pyrimidinium iodide*, which separated on cooling, crystallised from water as thick plates, m. p. 180—181° (Found: C, 41·6; H, 4·3; N, 11·5. $C_{12}H_{16}N_3SI$ requires C, 41·8; H, 4·3; N, 11·3%).

4-*Anilino*-1 : 2-*dimethyl*-6-*methylthiopyrimidinium Iodide* (VI; R = Me, R′ = SMe).—(*a*) 4-Chloro-6-methylthio-1 : 2-dimethylpyrimidinium iodide (3·16 g.), aniline (0·93 g.), and water (20 c.c.) were heated under reflux for 0·5 hr. A thick precipitate was formed immediately. The *pyrimidinium iodide* was collected and crystallised from 50% aqueous alcohol as short, flat prisms, m. p. 244—246° (decomp.) (Found: C, 41·9; H, 4·4; N, 11·4%).

(*b*) 6-Chloro-4-anilino-1 : 2-dimethylpyrimidinium iodide (2·3 g.), water (10 c.c.) and sodium methyl sulphide (3·1 c.c. of alcoholic 2M-solution) were mixed. Immediate reaction ensued and, next morning the product was collected and crystallised from 50% aqueous alcohol; it had m. p. and mixed m. p. 244—246° (decomp.).

4-*Anilino*-2-*methyl*-6-*methylaminopyrimidine* (VIII; R = Me).—(*a*) 4-Anilino-6-chloro-2-methylpyrimidine (2·1 g.) and alcoholic methylamine (50 c.c. of 35% solution) were heated in a sealed tube at 150—160° for 4 hr. The clear solution was evaporated to dryness and the residue dissolved in dilute hydriodic acid. 4-*Anilino*-2-*methyl*-6-*methylaminopyrimidine hydriodide* separated, forming plates m. p. 220—222°, from water (Found: C, 42·3; H, 4·25; N, 16·5. $C_{12}H_{14}N_4.HI$ requires C, 42·1; H, 4·1; N, 16·3%). Addition of ammonia to an aqueous solution precipitated the *base* which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 150° (Found: C, 67·55; H, 6·55; N, 25·95. $C_{12}H_{14}N_4$ requires, 67·3; H, 6·5; N, 26·1%).

(*b*) 4-Anilino-6-chloro-1 : 2-dimethylpyrimidinium iodide (1·95 g.) was mixed with liquid ammonia (15 c.c.) and kept for 60 hr. The ammonia was evaporated and the residue dissolved in dilute hydriodic acid. The pyrimidine hydriodide which separated was crystallised from water; it had m. p. and mixed m. p. 222—224°.

4-Anilino-2-methyl-6-methylaminopyrimidine was also obtained by the action of liquid ammonia on 4-anilino-1 : 2-dimethyl-6-methylthio- and by heating 4-anilino-6-chloro-1 : 2-dimethyl-, 4-anilino-1 : 2-dimethyl-6-methylthio-, or 6-amino-4-anilino-1 : 2-dimethylpyrimidinium iodide with alcoholic ammonia at 100—120°.

(*c*) 6-Amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (0·5 g.) was warmed in a solution of sodium carbonate (0·3 g.) in water (5 c.c.). An oil was deposited. After 4 hours' heating under reflux the mixture was cooled and the product collected and isolated as the hydriodide. Ammonia precipitated the base, m. p. and mixed m. p. 150—152° (from benzene).

(*d*) 6-Amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (0·8 g.), methanol (20 c.c.), and piperidine (3 c.c.) were heated together in a sealed tube for 5 hr. at 100°. The solution was evaporated to small bulk and ethyl acetate added. Piperidine hydriodide was precipitated. The liquors were evaporated to dryness and the residue extracted with ether. Evaporation of the ether solution gave 4-anilino-2-methyl-6-methylaminopyrimidine identical with material prepared by method (*a*).

4-Anilino-6-chloro-1-methylpyrimidinium Iodide (VI; R = H, R′ = Cl).—4 : 6-Dichloropyrimidine (Kenner, Lythgoe, Todd, and Topham *J.*, 1943, 575) (10·5 g.), aniline (6·9 c.c.), water (45 c.c.), acetone (30 c.c.), and concentrated hydrochloric acid (0·75 c.c.) were heated under reflux for 1·5 hr. The solid, which separated on cooling, was collected and dissolved in methanol; the methanol solution was made alkaline with ammonia and diluted with water. *4-Anilino-6-chloropyrimidine* was precipitated and crystallised from aqueous methanol as prisms, m. p. 154—156° (8·8 g.) (Found: C, 58·4; H, 3·7; N, 20·3. $C_{10}H_8N_3Cl$ requires C, 58·4; H, 3·8. N, 20·5%). 4-Anilino-6-chloropyrimidine (5·16 g.) was dissolved in nitrobenzene (50 c.c.) at 90—95° and methyl sulphate (6·5 c.c.) was added. After being stirred for 4·5 hr. at 90—95°, the nitrobenzene solution was cooled and extracted with water (3 × 50 c.c.). Addition of sodium iodide to the combined aqueous extracts precipitated *4-anilino-6-chloro-1-methylpyrimidinium iodide* (3·75 g.), plates, m. p. 196—197° (decomp.) (from water) (Found: C, 38·3; H, 3·3; N, 11·9. $C_{11}H_{11}N_3ClI$ requires C, 38·0; H, 3·2; N, 12·1%).

4-Anilino-6-methylaminopyrimidine (VIII; R = H).—(*a*) 4-Anilino-6-chloropyrimidine (2·0 g.) and methanolic methylamine (50 c.c.) were heated in a sealed tube at 150—160° for 5 hr. The contents of the tube were evaporated to dryness and the residue was dissolved in hot dilute hydriodic acid. Ammonia then precipitated *4-anilino-6-methylaminopyrimidine* which crystallised from aqueous methanol as plates, m. p. 206—207° (Found: C, 66·6; H, 5·95; N, 27·8. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%).

(*b*) 4-Anilino-6-chloro-1-methylpyrimidinium iodide (1·0 g.) and alcoholic ammonia (20 c.c. of saturated solution) were heated for 5 hr. in a sealed tube at 115—125°. The mixture was then filtered and the filtrate evaporated to dryness. The combined solids were dissolved in dilute hydrochloric acid and the acid solution was basified with ammonia. The precipitated 4-anilino-6-methylaminopyrimidine crystallised from aqueous methanol; it had m. p. and mixed m. p. 206—207°.

4-Anilino-6-chloro-1-methyl-2-phenylpyrimidinium Iodide (VI; R = Ph, R′ = Cl).—4-Chloro-6-hydroxy-2-phenylpyrimidine (prepared from 4 : 6-dichloro-2-phenylpyrimidine by hydrolysis with hydrochloric acid in butanol) (67·1 g.), aniline (30·8 g.), and concentrated hydrochloric acid (5·5 c.c.) were heated together for 6 hr. at 145—155°. The melt was cooled, ground, and stirred with 10% aqueous acetic acid (550 c.c.) and filtered. The solid was then treated with hot dilute aqueous ammonia (3%), filtered, and dried. *4-Anilino-6-hydroxy-2-phenylpyrimidine* thus obtained crystallised from 2-ethoxyethanol (yield, 50 g.). An analytical sample crystallised from alcohol as prisms, m. p. 209° (Found: C, 73·45; H, 5·2; N, 16·5. $C_6H_{12}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%).

4-Anilino-6-hydroxy-2-phenylpyrimidine (50 g.) and phosphoryl chloride (100 c.c.) were heated under reflux for 1 hr. The excess of phosphoryl chloride was evaporated under reduced pressure and the residue poured on ice. After basification with ammonia, the crude product was extracted with ether and the ethereal solution was shaken with dilute ammonia. After drying (Na_2SO_4), the ether was evaporated and the *4-anilino-6-chloro-2-phenylpyrimidine* crystallised from aqueous methanol as prisms, m. p. 132—134° (Found: C, 68·0; H, 3·85; N, 14·7. $C_{16}H_{12}N_3ClI$ requires C, 68·2; H, 4·3; N, 14·9%).

4-Anilino-6-chloro-2-phenylpyrimidine (5·0 g.) was dissolved in nitrobenzene (40 c.c.) at 90—95°. Methyl sulphate was added and the mixture was stirred at 90—95° for 4·5 hr. After cooling, the nitrobenzene was extracted with water (3 × 50 c.c.) and excess of sodium iodide was added to the combined aqueous extracts. *4-Anilino-6-chloro-1-methyl-2-phenylpyrimidinium iodide* was precipitated, forming needles (from 50% aqueous methanol), m .p. 164—166° (decomp.) (Found: C, 47·75; H, 3·85; N, 9·8. $C_{17}H_{15}N_3ClI$ requires C, 48·1; H, 3·54; N, 9·9%).

4-Anilino-6-methylamino-2-phenylpyrimidine (VIII; R = Ph).—(*a*) 4-Anilino-6-chloro-2-phenylpyrimidine (1·5 g.) and methanolic methylamine (25 c.c.) were heated in a sealed tube at

140—150° for 5 hr. The solution was evaporated to dryness, and the residue was dissolved in methanol and made acid with hydrochloric acid. The precipitated solid was collected, dissolved in 50% aqueous methanol, and made alkaline with ammonia. *4-Anilino-6-methylamino-2-phenylpyrimidine* was extracted with ether; crystallised from light petroleum (b. p. 100—120°), it had m. p. 126—128° (Found: C, 73·95; H, 5·8, N, 20·2. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·8; N, 20·2%).

(*b*) 4-Anilino-6-chloro-1-methyl-2-phenylpyrimidinium iodide (0·8 g.) and alcoholic ammonia (20 c.c. of saturated solution) were heated in a sealed tube for 5 hr. at 100°. The methanol solution was evaporated to dryness and the residue worked up as in (*a*) above. The pyrimidine had m. p. and mixed m. p. 126—128°.

4-Anilino-1: 2-dimethyl-6-methylaminopyrimidinium iodide (VI; R = Me, R′ = NHMe).—4-Anilino-1: 2-dimethyl-6-methylthiopyrimidinium iodide (1·0 g.) and methanolic methylamine (25 c.c. of 35% solution) were heated in a sealed tube at 100° for 5 hr. The solid which separated on cooling crystallised from water as needles, m. p. 240° (Found: C, 43·75; H, 4·75; N, 15·6. $C_{13}H_{17}N_4I$ requires C, 43·5; H, 4·7; N, 15·7%). The same compound was obtained from 4-anilino-6-chloro-1: 2-dimethylpyrimidinium iodide and alcoholic methylamine.

4-Amino-1: 2-dimethyl-6-(1: 2-dimethyl-6-methylthiopyrimidinium-4-amino)quinolinium Di-iodide (I; R = SMe).—4-Chloro-1: 2-dimethyl-6-methylthiopyrimidinium iodide (3·16 g.), 4: 6-diamino-1: 2-dimethylquinolinium iodide (3·16 g.), and water (15 c.c.) were heated under reflux for 30 min. After cooling, the solid was filtered off and dissolved in aqueous ethanol and the quaternary *di-iodide* was precipitated by the addition of sodium iodide. It crystallised from water, in which it was approximately 10% soluble at 100°, and when pure had m. p. 300—302° (decomp.) (Found: C, 36·35; H, 4·15; N, 11·4. $C_{18}H_{22}N_5SI_2$ requires C, 36·3; H, 3·9; N, 11·8%).

4-Amino-1: 2-dimethyl-6-(6-methylamino-1: 2-dimethylpyrimidinium-4-amino)quinolinium Di-iodide (I; R = NHMe).—4-Amino-1: 2-dimethyl-6-(1: 2-dimethyl-6-methylthiopyrimidinium-4-amino)quinolinium di-iodide (1·0 g.) and methanolic methylamine (20 c.c. of 21% solution) were heated for 7 hr. in a sealed tube at 100°. The quaternary *salt* was collected and, crystallised from water, had m. p. 312° (decomp.) (Found: C, 26·3; H, 4·6; N, 13·8. $C_{18}H_{24}N_6I_2.H_2O$ requires C, 36·2; H, 4·4; N, 14·1%).

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Researches on Acetylenic Compounds. Part XLIX. The Preparation and Ultraviolet Absorption Spectra of the Stereoisomeric Conjugated Hexadienoic and Hexenynoic Acids.*

By J. L. H. ALLAN, E. R. H JONES, and M. C. WHITING.

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All the possible stereoisomeric forms of the conjugated hexadienoic and hexenynoic acids have been prepared. Their properties, and in particular their ultraviolet absorption spectra, have been compared with those of hexa-2: 4-diynoic, but-2-ynoic, and the two but-2-enoic acids.

THE specificity of palladium catalysts, in particular the lead-poisoned form (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446), for the partial hydrogenation of acetylenic linkages has permitted syntheses of several conjugated polyenes with *cis*-linkages in predetermined positions. These products, however, have all been complex compounds related to the carotenoids, with the exception of the *cis-cis*- and *cis-trans*-diphenylbuta-1: 3-dienes prepared by Pinkard, Wille, and Zechmeister (*J. Amer. Chem. Soc.*, 1948, **70**, 1938), in which steric hindrance to the coplanarity of the chromophore is also involved. We now describe syntheses of the stereoisomers of *trans-trans*-hexa-2: 4-dienoic (sorbic) acid, and of the four related hexenynoic acids. These substances were chosen because they fairly represent

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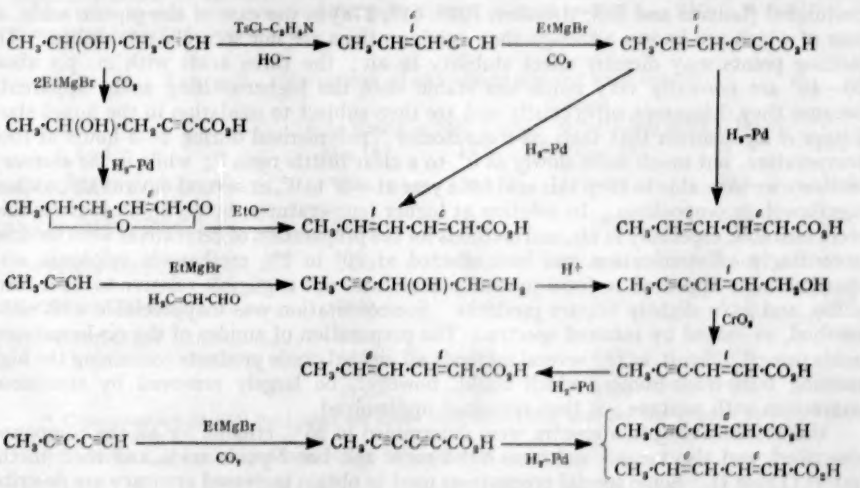
simple conjugated aliphatic *cis*-ethylenes, and would probably crystallise and so be obtainable pure even though unstable. The spectroscopic data reported here and in the following paper would also be useful in diagnostic problems involving naturally-occurring conjugated polyene and polyenyne esters. Parallel and independent work by Crombie (*J.*, 1955, 1007) on the synthesis of the decadienoic acids has recently been published.

Of the nine C_6-acids with ethylenic and/or acetylenic bonds in the $\alpha\beta$- and the $\gamma\delta$-position, the *trans-trans*-diene has been known for many years, and hexa-2 : 4-diynoic acid has been briefly described by Schlubach and Wolf (*Annalen*, 1950, **568**, 141) and by Jones, Whiting, Armitage, Cook, and Entwistle (*Nature*, 1951, **168**, 900), who treated the bromomagnesium derivative of penta-1 : 3-diyne with carbon dioxide. When *cis*- and *trans*-pent-3-en-1-yne (Allan and Whiting, *J.*, 1953, 3314) were treated similarly the *cis*- and *trans*-hex-4-en-2-ynoic acids were obtained. Semihydrogenation (Lindlar, *loc. cit.*) of the *cis*-acid readily gave hexa-*cis*-2 : *cis*-4-dienoic acid, m. p. 81·5—82·5°, while the *trans*-isomer gave the expected hexa-*cis*-2 : *trans*-4-dienoic acid, m. p. 31—34°, which was much less easily isolated. In the latter case a little *trans-trans*-hexadienoic acid was also obtained, in agreement with the view (see Raphael, "Acetylenic Compounds," Butterworth, 1955, p. 24) that a small proportion (~5%) of the *trans*-compound is normally formed in the semihydrogenation of acetylenic compounds. In both cases hexenoic and unchanged hexenynoic acids were present in the crude product, but could be removed by distillation and recrystallisation until melting point and infrared absorption spectrum were constant.

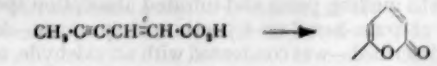
For the synthesis of *trans*-hex-2-en-4-ynoic acid, propyne—for which an improved preparative method is described—was condensed with acraldehyde, and the resulting alcohol was rearranged to hex-2-en-4-yn-1-ol, the *trans*-isomer being the main product (cf. Braude and Coles, *J.*, 1951, 2085). Oxidation with chromic and sulphuric acids in aqueous acetone (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586) gave the corresponding acid, whose *trans*-configuration, deduced from the method of synthesis, was confirmed by the infrared spectrum described in the following paper. Semihydrogenation gave hexa-*trans*-2 : *cis*-4-dienoic acid in fair yield.

Wholly rational routes to hexa-*cis*-2-en-4-ynoic acid seemed unpromising; yet this acid is a close model for a number of natural polyacetylenic esters [Wiljams, Smirnov, and



Golmov, *J. Gen. Chem.* (*U.S.S.R.*), 1935, **5**, 1195; Sörensen *et al.*, *Acta Chem. Scand.*, 1951, **5**, 1244; 1952, **6**, 883; 1954, **8**, 26], and its omission from the group of acids studied would be unfortunate. The tendency for carbonyl groups in polycyclic systems to facilitate the hydrogenation of adjacent ethylenic linkages (Stavely and Bollenback, *J. Amer. Chem.*

Soc., 1943, **65**, 1290; Bladon *et al.*, *J.*, 1953, 2921) suggested, however, that with hexa-2 : 4-diynoic acid the initial attack might be mainly on the Δ^2-linkage; furthermore studies of the dissociation constants of a number of unsaturated acids showed that *trans*-hex-2-en-4-ynoic acid (p*K* 4·1) could be separated fairly easily from all αβ-acetylenic acids (p*K* 1·6—2·6) and all non-acetylenic acids (p*K* *ca.* 4·7) by counter-current distribution. This reaction was therefore examined, although it was known (Riley, *J.*, 1953, 2193, and unpublished work from these laboratories) that catalytic hydrogenation of 1 : 3-diacetylenes does not normally give even moderate yields of vinylacetylenes. Counter-current distribution between a phosphate buffer and di*iso*propyl ether in a 24-tube apparatus, with 100 transfers, resulted in the isolation, at the extremes, of hexa-*cis*-2 : *cis*-4-dienoic acid (20%) and unchanged hexadiynoic acid (30%). In the intermediate tubes two other substances were identified; one, isolated in 0·5% yield, was clearly the desired hex-*cis*-2-en-4-ynoic acid, in view of analytical data and spectroscopic results. The other product (yield 0·2%) appeared from its infrared spectrum to be an unsaturated lactone; it had ultraviolet maxima at 2200 and 3010 Å, which may be compared with $\lambda_{max.}$ 2980 Å, ε = 5,000, quoted by Fried and Elderfield (*J. Org. Chem.* 1941, **6**, 566) for 5-methyl-α-pyrone. This substance must almost certainly be 6-methyl-α-pyrone, formed from the *cis*-hexenynoic acid by a cyclisation process subsequent to hydrogenation, probably catalysed by the considerable quantity of hexa-2 : 4-diynoic acid (p*K* 1·7) still present:



During the course of this work Eisner, Elvidge, and Linstead (*J.*, 1953, 1372) described the preparation of hexa-*cis*-2 : *trans*-4-dienoic acid by the action of sodium ethoxide on the lactone of 4-hydroxyhex-2-enoic acid. This reaction [cf. Jones and Whiting (*J.*, 1949, 143) for the closely analogous preparation of 2-methoxyhexa-2 : 4-dienoic acid] is undoubtedly better than the hydrogenation method described above for *cis*-2 : *trans*-4-dienoic acids.

The melting points of the various hexadienoic and hexenynoic acids (Table 1) clearly reveal the effects of molecular symmetry, in particular in that the *cis-cis*-hexadienoic acid melts much higher than either of the *cis-trans*-isomers. A similar relation has been postulated (Lohaus and Gill, *Annalen*, 1935, **517**, 278) in the case of the piperic acids, all four of which are known although their configurations are not securely established. The melting points may directly affect stability in air; the three acids with m. p.s about 30—40° are normally very much less stable than the higher-melting acids, apparently because they deliquesce superficially and are then subject to oxidation in the liquid state. Eisner *et al.* mention that their *cis-trans*-isomer " polymerised during 2—3 hours at room temperature, but much more slowly at 0°, to a clear brittle resin "; while *in the absence of moisture* we were able to keep this acid for a year at −5° to 0°, or several days at 15°, without significant decomposition. In solution at higher temperatures, however, all four *cis*-acids were unstable, especially in air, and methods for the preparation of derivatives were modified accordingly. Esterification was best effected at 20° in 2% methanolic sulphuric acid; diazomethane appeared to form pyrazolines at rates not negligible relative to ester formation, and gave slightly impure products. Stereomutation was inappreciable with either method, as judged by infrared spectra. The preparation of amides of the *cis*-hexadienoic acids proved difficult, as the several methods all yielded crude products containing the high-melting *trans-trans*-isomer, which could, however, be largely removed by continuous extraction with pentane; it then remained undissolved.

Ultraviolet absorption spectra were determined in 95% ethanol for all the compounds described, and also for *cis*- and *trans*-but-2-enoic and but-2-ynoic acids and their methyl esters (Table 1). Some special precautions used to obtain increased accuracy are described in the Experimental section. It was found that the hexa-2 : 4-dienoic acids fail to obey Beer's law accurately in some regions of the spectra (Table 2), the reason clearly being a difference between the spectra of the anion and of the uncharged molecule, the magnitude of the difference varying considerably from case to case. Such phenomena are common among enolic β-diketones, etc., but have not, as far as is known, been observed with simple

TABLE 1. *Absorption spectra in 95% ethanol.*

Acid	M. p.	Free acid $\lambda_{max.}$ (Å)	Free acid $10^{-3}\varepsilon$	Methyl ester $\lambda_{max.}$ (Å)	Methyl ester $10^{-3}\varepsilon$	Ref.
$CH_3{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	71—72°	2030	16·0	2045	16·5	1
		2460 *	0·15	2500 *	0·14	
$CH_3{\cdot}CH{=}^{c}CH{\cdot}CO_2H$	13·5—14·5	2055	13·5	2055	14·0	
		2420 *	0·25	2450 *	0·25	
$CH_3{\cdot}C{\equiv}C{\cdot}CO_2H$	76—77	2050	6·4	2055	7·2	
		2120 *	4·2	2120 *	4·8	
$CH_3{\cdot}CH{=}^{t}CH{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	132—134	2540	26·0	2585	26·5	2
$CH_3{\cdot}CH{=}^{c}CH{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	35—38	2600	22·5	2620	23·5	
$CH_3{\cdot}CH{=}^{t}CH{\cdot}CH{=}^{c}CH{\cdot}CO_2H$	31—34	2570	21·0	2605	21·5	3
$CH_3{\cdot}CH{=}^{c}CH{\cdot}CH{=}^{c}CH{\cdot}CO_2H$	81·5—82·5	2590	20·0	2635	19·0	
$CH_3{\cdot}C{\equiv}C{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	182—183·5	2455	16·0	2570	19·0	
$CH_3{\cdot}C{\equiv}C{\cdot}CH{=}^{c}CH{\cdot}CO_2H$	114—117·5	2440	11·0	2585	14·0	
$CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CO_2H$	130·5—132·5	2470	11·5	2500	13·0	
		2830 *	0·98	2860 *	1·5	
$CH_3{\cdot}CH{=}^{c}CH{\cdot}C{\equiv}C{\cdot}CO_2H$	33—35	2460	10·5	2490	11·5	
		2830 *	0·95	2860 *	1·0	
$CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CO_2H$	118—120	2200	1·1	2240	1·1	
		2340	1·8	2350	2·1	
		2460	3·1	2470	3·9	
		2590	4·1	2610	5·3	
		2750	2·7	2760	3·7	

* Inflexion.

References: (1) Hausser, Kuhn, Smakula, and Hoffer, *Z. phys. Chem.*, 1935, *B*, **29**, 371, give $\lambda_{max.}$ 2040 Å, $\varepsilon = 11{,}700$, for the acid. (2) For the acid, *idem*, *ibid.*, give $\lambda_{max.}$ 2540 Å, $\varepsilon = 24{,}800$, and Eisner *et al.* (*loc. cit.*) give $\lambda_{max.}$ 2570 Å, $\varepsilon = 27{,}400$ (and subsidiary bands). (3) Eisner *et al.* (*loc. cit.*) give $\lambda_{max.}$ 2570 Å, $\varepsilon = 17{,}000$ (and subsidiary bands) for the acid, and $\lambda_{max.}$ 2570 Å, $\varepsilon = 17{,}400$ (and subsidiary bands) for the ester.

All these spectra were determined in pure ethanol, in which we find $\lambda_{max.}$ 2560 Å, $\varepsilon = 27{,}000$, for *trans-trans*-hexa-2 : 4-dienoic acid.

TABLE 2. *Variations of absorption spectra with acidity.*

Acid	Solvent: 0·2N-NaOH in 76% EtOH $\lambda_{max.}$ (Å)	0·2N-NaOH in 76% EtOH $10^{-3}\varepsilon$	0·2N-H_2SO_4 in 76% EtOH $\lambda_{max.}$ (Å)	0·2N-H_2SO_4 in 76% EtOH $10^{-3}\varepsilon$	$10^4 c$ *
$CH_3{\cdot}CH{=}^{c}CH{\cdot}CH{=}^{c}CH{\cdot}CO_2H$	2500	17·5	2630	19·5	41·6
$CH_3{\cdot}CH{=}^{t}CH{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	2490	23·5	2585	26·0	37·2
$CH_3{\cdot}C{\equiv}C{\cdot}CH{=}^{t}CH{\cdot}CO_2H$	2470	15·5	2540 †	18·5	43·0
$CH_3{\cdot}CH{=}^{t}CH{\cdot}C{\equiv}C{\cdot}CO_2H$	2440	11·5	2490	12·5	59·8
$CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CO_2H$	2320	1·8	2350	2·1	123
	2440	2·5	2470	3·6	
	2560	2·55	2600	4·6	
	2720	1·8	2760	3·1	

* Concentration (g./100 c.c.) used for these determinations, and for the spectra in 95% ethanol reported in Table 1.

† Value of $\lambda_{max.}$ unchanged in acidified 95% ethanol.

carboxylic acids before, doubtless because maxima are flat and the shifts small. Curves for the methyl esters are illustrated in Figs. 1 and 2; those obtained for the free acids were similar (Table 1), and need not be discussed in detail. All results obtained for the *trans-trans-* and *cis*-2 : *trans*-4-acids and their derivatives, however, differ from those reported

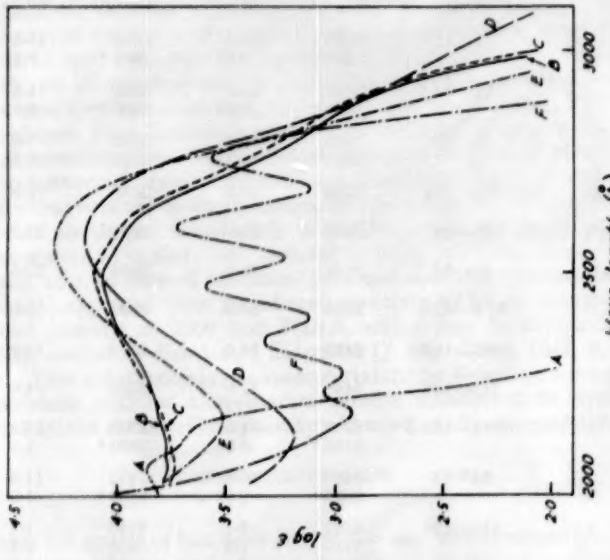


FIG. 2.

A, Methyl but-2-ynoate.
B, Methyl hex-*cis*-4-en-2-ynoate.
C, Methyl hex-*cis*-4-en-2-ynoate.
D, Methyl hex-*cis*-2-en-4-ynoate.
E, Methyl hex-*trans*-2-en-4-ynoate.
F, Methyl hexa-2 : 4-diynoate.

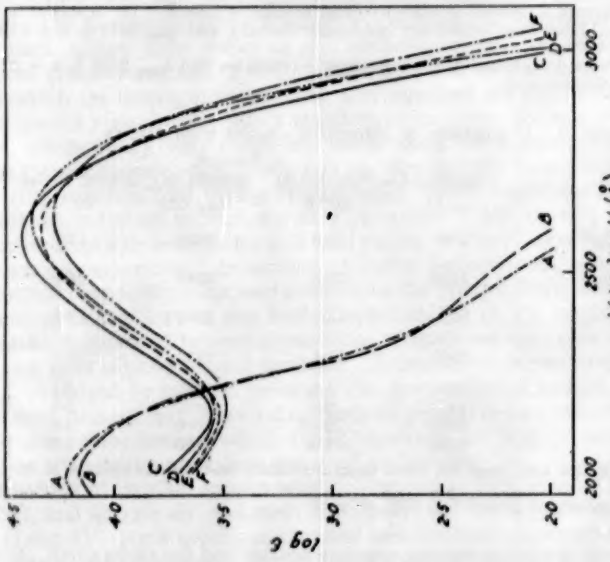


FIG. 1.

A, Methyl *trans*-but-2-enoate.
B, Methyl *cis*-but-2-enoate.
C, Methyl hexa-*trans*-2 : *trans*-4-dienoate.
D, Methyl hexa-*trans*-2 : *cis*-4-dienoate.
E, Methyl hexa-*cis*-2 : *trans*-4-dienoate.
F, Methyl hexa-*cis*-2 : *cis*-4-dienoate.

by Eisner *et al.* (*loc. cit.*) in that in every case only one broad maximum was observed, without subsidiary maxima, inflexions, or even noticeable "shoulders," whereas Eisner *et al.* found groups of two or three maxima in most instances. This discrepancy is not due to the change of solvent (100% instead of 95% ethanol) although intensity readings for sorbic acid in 100% ethanol were a little higher than in 95% ethanol, probably because ionisation was repressed; nor could it be due to lack of resolution in the photoelectric spectrophotometer used here, which easily resolves fine structure closer than that reported. Dr. E. A. Braude has very kindly reinvestigated some of these spectra, using a photoelectric instrument, and also using the original photographic instrument, but with a smaller optical-density interval between match-points, and finds that these "maxima" are unreal. The effect is apparently an optical illusion in reading the plate, connected with the line emission spectrum of the iron arc, and is evidently a danger when compounds with flat maxima are studied by the photographic method. (On the other hand, polyenes and similar substances frequently show genuine subsidiary maxima or inflexions, and casual use of a photoelectric instrument, with readings taken at wide wavelength intervals, might well fail to detect them.) In the case of *trans-trans*-hexa-2 : 4-dienoic acid the absence of subsidiary maxima or inflexions was finally confirmed by using a recording photoelectric instrument of very high resolving power.

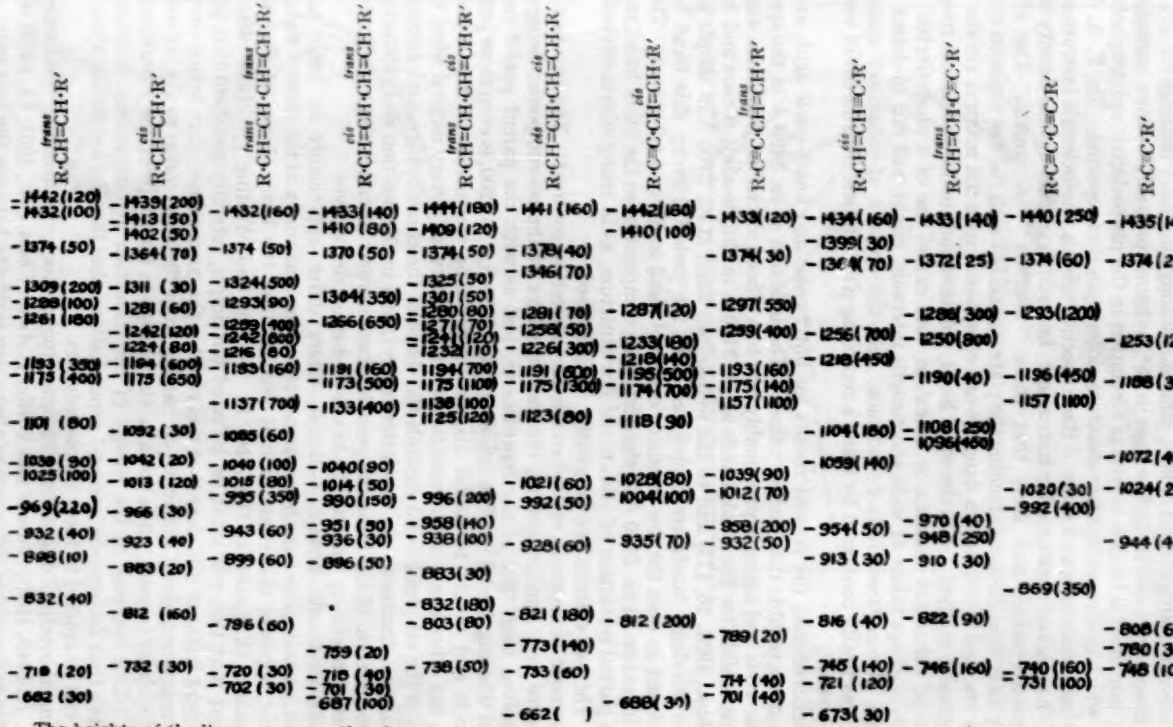
It is believed that the present results for but-2-enoic and but-2-ynoic acids and their esters are more reliable than earlier values. The inflexion at *ca.* 2400 Å in the spectra of but-2-enoic acids and esters is presumably due to a second electronic transition, analogous to that responsible for the weak bands at *ca.* 2100 Å in simple acids (Cason and Sumrell, *J. Org. Chem.*, 1951, **16**, 177) and to the well-known band at *ca.* 2700 Å in simple ketones. When two ethylenic bonds are conjugated with the carboxyl group this band becomes submerged just as does the low-intensity carbonyl band in di- and tri-enones. The high-intensity inflexions at *ca.* 2130 Å in the acetylenic compounds, on the other hand, may well be due to partial resolution of vibrational fine structure, as in many vinylacetylenic compounds. The two systems are thus easily distinguished.

The isomeric hexenynoic esters provide an interesting contrast. The two hex-4-en-2-ynoates show very similar spectra, the fine structure of the *cis*-compound being a little better resolved than that of the *trans*-isomer, just as with the parent pent-3-en-1-ynes (Allan and Whiting, *loc. cit.*). The inflexion at ca. 2850 Å, $\varepsilon = 1200$, is even more prominent in the acids and should be useful diagnostically. The stereoisomeric hex-4-yn-2-enoic esters, on the other hand, differ considerably in intensity, as is very natural when the configuration of the ethylenic bond controls the shape of the chromophore, and neither shows vibrational fine structure. In this latter respect, and in the position and intensity of the absorption maxima of the *trans*-compounds, these isomers resemble the hexa-2 : 4-dienoic derivatives more closely than do the hex-2-yn-4-enoic derivatives.

The stereoisomeric hexa-2 : 4-dienoic esters differ appreciably in both $\lambda_{max.}$ and absorption intensity, the *trans-trans*-isomer absorbing maximally at the *shortest* wavelength, exactly the opposite behaviour to that predicted on the basis of one of Zechmeister's generalisations (*Experientia*, 1954, **10**, 1). Nayler and Whiting (*J.*, 1954, 4006) have pointed out that this rule must be inverted for simple, laterally-unsubstituted polyenes. In the present instance it is clear that this result is the consequence of an actual decrease in the electronic energy-level difference on passing from the *trans-trans*- to the *cis-trans*- and then to the *cis-cis*-isomers; it is not a trivial change in the shape of the vibrational band-envelope. This decrease in the energy of the transition accompanies a decrease in its probability; thus Zechmeister's second generalisation, that the all-*trans*-isomer absorbs most strongly, can be applied to these simple polyenes.

Existing theoretical discussions (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403) cover the appreciable and variable difference in absorption intensity between the four pairs of esters differing in configuration at the Δ^2-linkage; in each *cis*-form interference with the coplanarity of the ethylenic linkage and the ester grouping, especially in the preferred *transoid* conformation, may be envisaged, although in the case of hex-*cis*-2-en-4-ynoic ester the influence of the $CH_3 \cdot C \equiv C \cdot$ grouping might be predominantly electrostatic, rather than

FIG. 3.



The heights of the lines are proportional to the frequency of maxima (cm.$^{-1}$), given numerically alongside. Figures in parentheses are the corresponding ϵ values. R = CH_3. R′ = $\cdot CO_2CH_3$.

steric. The *trans* : *cis* intensity ratios for the three pairs of isomers differing at the Δ^4-linkage, however, are not so easily explained. Whereas the *cis*- and *trans*-forms of penta-1 : 3-diene and pent-3-en-1-yne absorb with practically equal intensity, extension of the chromophore by addition of a methoxycarbonyl group in each case results in an appreciable difference between geometrical isomers, the ratio showing a remarkable consistency (Table 3). Steric inhibition of resonance can be discounted here, since strainless planar

TABLE. 3. *Intensity ratios of stereoisomeric esters.*

Differing at Δ^2-linkage.	
trans-But-2-enoic : *cis*-but-2-enoic	1·18 (±0·05)
Hexa-*trans*-2 : *trans*-4-dienoic : hexa-*cis*-2 : *trans*-4-dienoic	1·23 (±0·02)
Hexa-*trans*-2 : *cis*-4-dienoic : hexa-*cis*-2 : *cis*-4-dienoic	1·24 (±0·02)
Hexa-*trans*-2-en-4-ynoic : hexa-*cis*-2-en-4-ynoic	1·35 (±0·03)
Differing at Δ^4-linkage.	
Hexa-*trans*-2 : *trans*-4-dienoic : hexa-*trans*-2 : *cis*-4-dienoic	1·13 (±0·02)
Hexa-*cis*-2 : *trans*-4-dienoic : hexa-*cis*-2 : *cis*-4-dienoic	1·13 (±0·02)
Hexa-*trans*-4-en-2-ynoic : hexa-*cis*-4-en-2-ynoic	1·13 (±0·02)
trans-Penta-1 : 3-diene : *cis*-penta-1 : 3-diene	1·02 *
trans-Pent-3-en-1-yne : *cis*-pent-3-en-1-yne	0·97 (±0·03) †

* Braude and Coles, *J.*, 1951, 2085. † Allan and Whiting, *loc. cit.*

models for every ester can be constructed even when van der Waals radii [which, as Braude *et al.* (*loc. cit.*) have shown, overstate the magnitude of steric interaction] are employed. Apparently other factors—perhaps differential solvation, for example—are involved, although their nature is not yet evident; and the present results accordingly emphasise the need for caution in ascribing to steric hindrance small differences of intensity of absorption between stereoisomers.

Infrared spectra for the acids and esters reported above are discussed in the following paper, in so far as correlation with other related substances is possible. Many bands which cannot yet be assigned should prove useful in recognising the various terminal groupings as complete units, since spectra are probably to a large extent independent of the length of the alkyl groups; this belief was confirmed by examination of Crombie's data. Accordingly, our results for the spectra of the esters in the 660—1450 cm.$^{-1}$ region are illustrated in Fig. 3; acids and amides gave generally similar results, with the obvious exceptions of bands attributable to the functional groupings concerned.

EXPERIMENTAL

M. p.s were determined on the Kofler block and are corrected; b. p.s are uncorrected; distillations were effected in the absence of oxygen, refractive indices being constant over at least 3 fractions (except where less than 50 mg. were involved) in cases where no range is quoted. Nitrogen was purified by Fieser's method (*J. Amer. Chem. Soc.*, 1924, **46**, 2639). Low-temperature crystallisations were carried out by gradually cooling solutions from room temperature to −25° (solid carbon dioxide–carbon tetrachloride) or −70° (solid carbon dioxide–acetone), removing the mother-liquors with a pipette, washing with precooled solvent, withdrawn similarly, and finally drying at 20 mm. in a desiccator in a refrigerated room (−5°) in dim light. Ultraviolet absorption spectra were determined, usually in 95% ethanol, with a Unicam S.P. 500 spectrophotometer, a new (life >100 hr.) hydrogen discharge tube being used when the 2000—2050 Å region was examined. The percentage of scattered light (only up to 1% at 2000 Å) was estimated and corrected for by the method of Eglinton, Jones, and Whiting (*J.*, 1952, 2873). Cleanliness of cell faces proved to be extraordinarily important in this region. Cylindrical Hilger cells (1 mm.) were used, and small (>5%) variations in intensity were observed according to their orientation, an arbitrary, but roughly average, position being employed consistently for work at short wavelengths. The precision of the results may be judged by the following replicate values for $\lambda_{max.}$ (Å) and $10^{-3}\varepsilon$; *trans*-but-2-enoic acid 2030 (16·0), 2030 (16·1); methyl *cis*-but-2-enoate, 2055 (13·9), 2055 (14·2); hexa-*cis*-2 : *trans*-4-dienoic acid, 2570 (20·8), 2570 (20·9), 2580 (21·3); hexa-*trans*-2 : *cis*-4-dienoic acid, 2600 (22·4), 2600 (22·6);

hexa-*trans*-2 : *trans*-4-dienoic acid, 2540 (26·0), 2540 (25·8); methyl hex-*trans*-4-en-2-ynoate, 2495 (12·7), 2505 (12·8); methyl hex-*trans*-2-en-4-ynoate, 2570 (18·6), 2570 (19·2). These are independent measurements on different samples; there were, however, cases where agreement between duplicate ultraviolet and infrared spectra of crystalline acids was less satisfactory because purification was incomplete, and with these recrystallisation was continued until the results became consistent.

Partial Reduction of Acetylenic Acids. General Method.—The acid, in the appropriate solvent, was shaken in hydrogen with Lindlar's catalyst (*loc. cit.*) (30·0 g. per mole of C≡C) and quinoline (10·0 g. per mole of C≡C), and the reaction was interrupted after the uptake of 1 mol. The acetylenic acid, when insoluble, passed into solution as the hydrogenation proceeded. After addition of ether (*ca.* one-third of the volume of the suspension), the catalyst was filtered off and the filtrate washed with 20% sulphuric acid saturated with potassium hydrogen sulphate (4 × 500 c.c. per mole) and dried ($MgSO_4$). Evaporation of the solvent at 20 mm. in a stream of nitrogen or carbon dioxide at room temperature afforded the crude acid.

trans-*Hex*-4-*en*-2-*ynoic acid.*—*trans*-Pent-2-en-4-yne (4·0 g.) was converted into an ethereal solution (200 c.c.) of its Grignard derivative which was added to a large excess of powdered carbon dioxide and set aside overnight, moisture being excluded by a " Cellophane " membrane. The resulting complex was decomposed by addition of 2N-sulphuric acid (ice), and the aqueous phase saturated with sodium chloride and thoroughly extracted with ether. The acid fraction, isolated *via* N-sodium hydroxide, afforded trans-*hex*-4-*en*-2-*ynoic acid* (3·3 g., 55%) as needles, m. p. 126—130°, after sublimation at 80—100° (bath temp.)/5 × 10^{-5} mm., raised to 130·5—132·5° (sublimes *ca.* 105°) by further recrystallisations from light petroleum (b. p. 80—100°) (Found: C, 65·35; H, 5·1. $C_6H_6O_2$ requires C, 65·45; H, 5·45%). The *methyl ester* had b. p. 105—110° (bath temp.)/20 mm., n_D^{25} 1·4868—1·4870, m. p. 14—16° (Found: C, 68·15; H, 6·85. $C_7H_8O_2$ requires C, 67·75; H, 6·45%).

cis-*Hex*-4-*en*-2-*ynoic Acid.*—When the above method was used, *cis*-pent-2-en-4-yne (13·5 g.) gave cis-*hex*-4-*en*-2-*ynoic acid* (8·4 g., 37%) as hygroscopic, elongated plates, m. p. 33—35° (uncorr.), after sublimation at 40—50° (bath temp.)/0·05 mm. and several recrystallisations from pentane at −6° (Found: C, 65·75; H, 5·55%). The *methyl ester*, which rapidly became yellow in air, had b. p. 75—80° (bath temp.)/18 mm., n_D^{25} 1·4802—1·4804 (Found: C, 67·75; H, 6·7%).

Propyne (with D. Bird and P. C. Wailes).—Sodamide was prepared from sodium (380 g., 16·5 mole) in liquid ammonia (8 l.). The temperature of the suspension was reduced to −60° and 1 : 2-dichloropropane (565 g., 5 mole) was forced into the stirred mixture by air pressure during 45 min. After a further 30 min. the cooling bath was removed and the ammonia was allowed to evaporate, final traces being removed on a steam-bath. The stirrer gland was then wired gas-tight and the flask was fitted with a gas outlet tube which led successively through two scrubbers containing 2N-sulphuric acid (total of 1 l.; containing phenolphthalein), two drying towers (KOH), two traps, each of 500-c.c. capacity and cooled to −60°, and a guard tube (KOH). The residual sodium salt was decomposed by the addition of 2N-sulphuric acid (2 l.; forced in by air pressure, slowly at first) during 1 hr., the flask being tipped manually to mix the reactants and control the rate of gas evolution. At this stage the flask and scrubbing solutions became quite hot. The apparatus was finally swept out with a stream of dry nitrogen, and the propyne, nearly all of which was in the first trap, was rapidly transferred to a small dry pre-cooled (−60°) metal cylinder which was finally sealed. The product from two such experiments weighed 346 g. (87%).

Hex-1-*en*-4-*yn*-3-*ol.*—(*a*) Propyne (40 g.; as above) was passed during 1 hr. into a solution of ethylmagnesium bromide (from 27 g. of magnesium) in ether (300 c.c.) in a flask fitted with an efficient reflux condenser surmounted by a carbon dioxide–acetone cooling finger. The stirred solution was then heated under reflux in a nitrogen atmosphere during 5 hr. and, after cooling, acraldehyde (62 g.; 74 c.c.) in ether (300 c.c.) was added during 2 hr. After the solution had been stirred for a further hour, saturated aqueous ammonium chloride (250 c.c.) was added followed by ice-cold 5% sulphuric acid until the emulsion was dispersed. Isolation and distillation gave the *alcohol* (54 g., 56%), b. p. 84—86°/60 mm., n_D^{19} 1·4710—1·4697. An analytical sample had n_D^{20} 1·4705 (Found: C, 74·9; H, 8·45. C_6H_8O requires C, 75·0; H, 8·3%). Light absorption: No maximum above 2200 Å with $E_{1\,cm.}^{1\%} > 20$. The *α-naphthylurethane* formed needles, m. p. 83·5—84·5°, from light petroleum (b. p. 60—80°) (Found: C, 76·9; H, 5·55; N, 5·35. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·65; N, 5·3%).

(*b*) 1 : 2-Dibromopropane (465 g.) was added to a vigorously stirred solution of potassium hydroxide (400 g.) in butanol (900 c.c.) heated under reflux, and the evolved propyne, after being passed through a drying tower ($CaCl_2$), was bubbled into ethylmagnesium bromide (from 49 g. of

magnesium) in ether (900 c.c.). Subsequent reaction of the Grignard derivative with acraldehyde (102 g.; 122 c.c.) and isolation in the manner described above gave the alcohol (97 g., 45% from the dibromide), b. p. 69—71°/40 mm., n_D^{24} 1·4680—1·4690.

Hex-2-en-4-yn-1-ol.—The above alcohol (42·0 g.) was shaken with sulphuric acid (420 c.c.; 15% w/v) in nitrogen during 44 hr. Isolation of the product with ether and distillation gave the *alcohol* (27·0 g., 64%), b. p. 82—84°/8 mm., n_D^{21} 1·5022—1·5030. An analytical sample had n_D^{22} 1·5080 (Found: C, 74·8; H, 8·05%). Light absorption: Max., 2250 Å; ε = 14,000. The *α-naphthylurethane* separated from light petroleum (b. p. 80—100°) in fine needles, m. p. 126—128° (Found: C, 77·5; H, 5·8; N, 5·5%).

trans-*Hex-2-en-4-ynoic Acid.*—Chromic acid solution (167 c.c.; 6N in 12N-sulphuric acid) was added, with stirring and cooling, to hex-2-en-4-yn-1-ol (24·0 g.) during 30 min. at 10—15°. The product was isolated in the usual way *via* N-sodium hydroxide, aqueous solutions being salted out at each stage. trans-*Hex-2-en-4-ynoic acid* (6·7 g., 25%; m. p. 165—175°) was obtained as needles, m. p. 182—183·5°, after several crystallisations from benzene–light petroleum (b. p. 80—100°) and sublimation at 90° (bath temp.)/0·01 mm. (Found: C, 65·2; H, 5·6%). The *methyl ester* had b. p. 70—75°/20 mm., n_D^{26} 1·4991—1·4987, m. p. 21·5—23·5° (Found: C, 67·65; H, 6·45%).

Penta-1 : 3-diyne.—This method is an improvement on that described by Armitage, Jones, and Whiting (*J.*, 1952, 1993). 1 : 4-Dichlorobut-2-yne (154 g.) was added during 1 hr. to a suspension of sodamide (from sodium, 89 g.) in liquid ammonia (2 l.) under reflux (carbon dioxide–acetone cooling finger). After 15 min., methyl iodide (177 g.) was added during 1 hr., and the mixture was stirred under reflux for a further 4 hr. Dry ammonium chloride (20 g.) was then added, followed by water (*ca.* 1·5 l.) at a rate such that the boiling ammonia could be condensed. When the reaction had completely subsided, the aqueous ammonia was cautiously extracted with commercial *iso*butane, and the combined extracts (800 c.c.) were kept at −5° overnight. Hexa-2 : 4-diyne crystallised and was separated from the solution by decantation. The bulk of the *iso*butane was removed from the decantate under partial reflux (CO_2–CCl_4) through a 20″ column packed with Dixon gauze rings ($\frac{1}{16}$″ × $\frac{1}{16}$″), and the remainder through a similarly-packed 6″ column until the head temperature reached 68°. Distillation of the residue at 20°/13 mm. into a cooled trap gave crude penta-1 : 3-diyne (29 g., 47%), n_D^{21} 1·4648 (Armitage *et al.*, *loc. cit.*, give b. p. 76·5°/742 mm., n_D^{15} 1·4790). The distillation residue was extracted with ether, and the dried ($MgSO_4$) extract combined with the hexa-2 : 4-diyne separated earlier. Removal of the ether through a 12″ Fenske column gave a residue which, after crystallisation from pentane at 0° and sublimation at 40° (bath temp.)/17 mm., afforded hexa-2 : 4-diyne (10·3 g., 11%), m. p. 66—67° (Armitage, Jones, and Whiting, *J.*, 1951, 44, give m. p. 67°). Penta-1 : 3-diyne cannot be distilled at atmospheric pressure without serious loss by polymerisation, and is more conveniently used without purification.

Hexa-2 : 4-diynoic Acid (with J. B. Armitage).—Crude penta-1 : 3-diyne (9·9 g.) was added to ethylmagnesium bromide (from 5 g., 1·4 equiv., of magnesium) in ether (150 c.c.), and the mixture was stirred and heated under reflux in nitrogen for 3 hr. The cooled solution was added to a large excess of powdered carbon dioxide in an autoclave (capacity 1800 c.c.) which was then sealed and kept at 20° overnight. The Grignard complex was decomposed with ice and 3N-sulphuric acid, and the product isolated in the manner usual for a water-soluble acid. *Hexa-2 : 4-diynoic acid* (11·0 g., 66%), m. p. 118—120°, formed flat needles, slightly yellow, after one crystallisation from benzene; a colourless sample, m. p. 118—120°, was obtained by sublimation at 80—85° (bath temp.)/0·01 mm. (Found: C, 66·35; H, 3·85. $C_6H_4O_2$ requires C, 66·65; H, 3·7%). The *methyl ester* had b. p. 30°/0·01 mm., n_D^{19} 1·5152—1·5159 (Found: C, 68·4; H, 5·2. $C_7H_6O_2$ requires C, 68·85; H, 4·9%).

Partial Catalytic Reduction of Hexa-2 : 4-diynoic Acid.—The acid (3·95 g.) in ethyl acetate (200 c.c.) was hydrogenated by the general method, the reaction being stopped after the uptake of 920 c.c. (1 mol.) of hydrogen at 23°/751 mm. The crude product (3·65 g.), a semi-crystalline yellow oil, was used (3·35 g.) directly for countercurrent partition in a 24-tube apparatus, with 80 c.c. and 40 c.c. of lower and upper phase, respectively, per tube (Craig and Craig, in Weissberger, "Technique in Orangic Chemistry," Interscience Inc., New York, 1950, Vol. III, p. 171—311). Preliminary volumetric results showed that the gross partition ratio between di*iso*propyl ether and M-phosphate buffer (pH 5·6) was 1·5 and these solvents were therefore selected, the ether being redistilled immediately before use. By the "single-withdrawal" technique 100 transfers were made, 77 raffinate fractions (denoted "fractions 1—77" in order of withdrawal) being collected. The contents of the 24 tubes were then isolated by strongly acidifying each aqueous layer, re-equilibrating with the di*iso*propyl ether, and again extracting the

aqueous layer with fresh ether; the combined ether extracts from each tube are denoted " tubes 1—24," numbering from the end at which the acid mixture was introduced. The absorption spectra in the region 2400—3100 Å, of representative eluted fractions and final upper phases of the tubes were determined, after suitable dilution with purified 95% ethanol, against solvents of the same composition. Relative transmission densities are summarised graphically in Fig. 4.

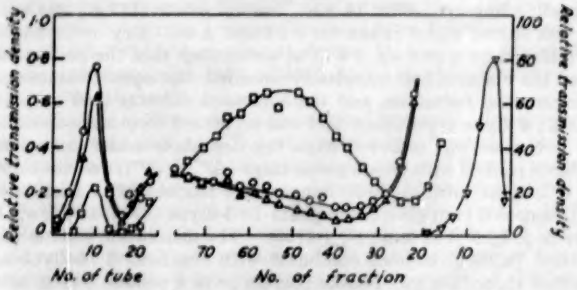
(*a*) Tubes 1—14 afforded hexa-2 : 4-diynoic acid (1·21 g., 33%), m. p. and mixed m. p. 116—118°. Tubes 1—4 also contained yellow polymeric material.

(*b*) Tubes 15—24 and fractions 69—77 afforded, after sublimation at 80—90° (bath temp.)/ 2×10^{-3} mm. and five crystallisations from light petroleum (b. p. 80—100°), *hex*-cis-2-*en*-4-*ynoic acid* (19·5 mg., 0·5%), m. p. 114—117·5°, as serrated plates, 5 mm. across (Found: C, 64·95; H, 5·6%). Its melting point and ultraviolet absorption spectrum were unchanged after three further crystallisations.

(*c*) From the yellow oil, isolated from fractions 60—68, more *cis*-hex-2-en-4-ynoic acid (0·65 mg.), m. p. 111—117°, undepressed on admixture with a sample from (*b*) above, was obtained after four crystallisations.

(*d*) The crude material from fractions 30—59 was distilled to give a yellow oil (15 mg.), b. p. 120—125° (bath temp.)/21 mm., n_D^{21} 1·5175, which, after seven recrystallisations from

FIG. 4.



Transmission density at: △, 2440 Å (left-hand scale); □, 3000 Å (left-hand scale); ○, ▽, 2570 Å (left- and right-hand scales, respectively).

pentane at −60°, afforded 6-*methyl*-α-*pyrone* (7·4 mg., 0·2%), m. p. 13—21°, n_D^{21} 1·5175 (Found: C, 65·05; H, 6·35. $C_6H_6O_2$ requires C, 65·45; H, 5·45%). Its infrared spectrum included bands at 1751 cm.$^{-1}$ (ε = 800), 1644 cm.$^{-1}$ (ε = 160), and 789 cm^{-1} (ε = 350), assigned to C=O stretching, C=C stretching, and *cis*–CH=CH– (conjugated) out-of-plane deformation modes, but lacked those expected for carboxyl groupings.

(*e*) Fractions 1—29 afforded *cis-cis*-hexa-2 : 4-dienoic acid (see below) (0·70 g., 19%), m. p. 75—82°, raised to 79—83·5° by further crystallisation, and undepressed on admixture with authentic material. Fractions 1 and 2 also contained yellow polymeric material.

Methyl cis-*hex*-2-*en*-4-*ynoate*.—*cis*-Hex-2-en-4-ynoic acid (11·0 mg.) in dry, freshly distilled ether (2 c.c.) was treated with a dry, freshly distilled ethereal solution of diazomethane (0·74 c.c.; 1·05 equiv.), and the mixture was set aside at 20° for 45 min. Evaporation of the ether and distillation of the residue in an Emich tube gave the *ester* (8·3 mg., 67%) as a single fraction, b. p. 75—80° (bath temp.)/17 mm., $n_D^{21.5}$ 1·5008 (Found: C, 67·7; H, 6·2%). Unchanged acid (0·70 mg., 6%), which had sublimed subsequently, was recovered and identified by its infrared spectrum.

Hexa-cis-2 : trans-4-*dienoic Acid*.—A suspension of *trans*-hex-4-en-2-ynoic acid (4·00 g.) in purified *n*-hexane (500 c.c.) was partially hydrogenated by the general method; uptake of hydrogen was 910 c.c. at 25°/745 mm. Crystallisations of the crude product from pentane, at −20 and −60°, afforded *hexa*-cis-2 : trans-4-*dienoic acid* (3·10 g., 76%) as needles, m. p. 25—31° (uncorr.), raised to 31—34° (uncorr.) by distillation (b. p. 58—60°/0·05 mm.) and further crystallisation at −60° (Eisner *et al.*, *loc. cit.*, give m. p. 32—35°) (Found: C, 64·65; H, 7·0. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·15%). The methyl ester had b. p. 51—53°/13 mm., n_D^{22} 1·4958 (Eisner *et al.* give b. p. 60°/11 mm., n_D^{22} 1·4948) (Found: C, 66·7; H, 7·95. Calc. for $C_7H_{10}O_2$:

C, 66·65; H, 7·95%). The amide, prepared from the pure acid by the method of Eisner *et al.*, was found to be contaminated with some of the *trans-trans*-isomer. The latter was largely removed by repeated partial sublimation at 50—60° (bath temp.)/0·01 mm. or partial extraction (Soxhlet) with warm pentane, when the higher-melting sorbamide remained unsublimed or undissolved. The desired amide was then crystallised twice from ethyl acetate–light petroleum, giving a product, m. p. 110—116° (Found: C, 64·55; H, 8·1. Calc. for C_6H_9ON: C, 64·85; H, 8·1%). Eisner *et al.* give m. p. 114°; a sample kindly supplied by Dr. J. A. Elvidge had undergone partial decomposition, but after recrystallisation it had m. p. 108—116°, undepressed on admixture with the product obtained as above. Light absorption (our sample): $\lambda_{max.}$ 2550 Å; ε = 22,000 (Eisner *et al.* give $\lambda_{max.}$ 2510 and 2570 Å; ε = 22,200).

Hexa-cis-2: cis-4-*dienoic Acid and its Derivatives.*—*cis*-Hex-4-en-2-ynoic acid (2·40 g.) in purified *n*-hexane (500 cc.) was partially hydrogenated by the general method, the reaction being interrupted when hydrogen absorption became extremely slow, after uptake of 440 c.c. (0·9 mol.) at 25°/762 mm. The crude product was crystallised twice from light petroleum (b. p. 60—80°) affording cis-cis-*hexadienoic acid* (1·28 g., 52%) as flat needles, m. p. 81·5—82·5° (Found: C, 64·3; H, 7·4%). The *methyl ester* had b. p. 80—85° (bath temp.)/20 mm., n_D^{23} 1·4933 (Found: C, 66·4; H, 7·75%). The *amide*, prepared as above, formed needles, m. p. 81—86°, after sublimation at 90—100° (bath temp.)/0·01 mm. and five crystallisations from ethyl acetate—light petroleum (b. p. 60—80°) (Found: C, 64·8; H, 8·4%). Light absorption: $\lambda_{max.}$ 2555 Å, ε = 22,000.

Hexa-trans-2: cis-4-*dienoic Acid.*—Hex-*trans*-2-en-4-ynoic acid (3·51 g.), in purified *n*-hexane (400 c.c.) and ethyl acetate (30 c.c.), was partially hydrogenated by the general method, permitted hydrogen uptake being 790 c.c. at 22°/760 mm. A solution of the crude product (2·90 g., 82%) in pentane (*ca.* 7 c.c.) deposited starting material (0·15 g., 4%), m. p. and mixed m. p. 165—176°, when cooled to −4° overnight. Cooling to −60° gave a second crop of crystals which, after distillation [b. p. 60—70° (bath temp.)/0·005 mm.] and four further crystallisations at −60°, afforded *hexa*-trans-2: cis-4-*dienoic acid* (1·65 g., 46%) as stout needles, m. p. 35—38° (Found: C, 64·0; H, 7·25%). The *methyl ester* had b. p. 85—90° (bath temp.)/20 mm., n_D^{21} 1·5003 (Found: C, 66·95; H, 7·85%). The *amide*, prepared by the above method, was obtained as needles, m. p. 89—93°, after partial sublimation at 80—100° (bath temp.)/0·01 mm., two partial extractions (Soxhlet) with warm pentane, and three crystallisations from ethyl acetate–light petroleum (b. p. 60—80°) (Found: C, 64·75; H, 7·85%). Light absorption: $\lambda_{max.}$ 2590 Å; ε = 24,000.

cis-*But*-2-*enoic Acid.*—A suspension of but-2-ynoic acid (3·03 g.; Henbest, Jones, and Walls, *J.*, 1950, 3646) in purified *n*-hexane (200 c.c.) was partially hydrogenated by the general method 910 c.c. of hydrogen being absorbed at 22°/751 mm. *cis*-But-2-enoic acid (1·48 g., 48%) formed prisms, m. p. 12·5—14·5°, from pentane at −60°, and had b. p. 70—70·5/17 mm., n_D^{19} 1·4455—1·4458 [Hatch and Nesbit (*J. Amer. Chem. Soc.* 1950, **72**, 727) give m. p. 13·5—13·8°, b. p. 54—55°/5 mm., n_D^{20} 1·4450]. The methyl ester had b. p. 102—104°/754 mm., n_D^{20} 1·4225 [Burki (*Helv. Chim. Acta*, 1918, **1**, 246) gives b. p. 119°] (Found: C, 60·0; H, 8·2. Calc. for $C_5H_8O_2$: C, 60·0; H, 8·0%).

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Researches on Acetylenic Compounds. Part L. The Infrared Absorption of Some Conjugated Ethylenic and Acetylenic Systems.*

By J. L. H. Allan, G. D. Meakins, and M. C. Whiting.

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From the infrared spectra of various types of conjugated ethylenic and acetylenic compounds, correlations facilitating the recognition of these systems have been established. Study of the 1050—650 cm.$^{-1}$ region yielded more detailed information than that obtained from the higher frequency ranges. In many of the compounds investigated geometrical isomerism is possible: examination of both *cis*- and *trans*-isomers led to useful spectral distinctions between them.

Other correlations relate to acetylenic compounds in which the triple bond is conjugated with acid or ester groups, and to halides of the allylic and propargylic types.

Although much information about the infrared absorption of compounds containing isolated multiple bonds is available in the literature, conjugated systems have received less attention. Past studies have dealt mainly with higher frequency ranges (above 1500 cm.$^{-1}$), which contain the easily recognised stretching vibrations. While the results are useful in detecting conjugation they are not sufficiently sensitive to provide clear distinctions between closely related systems. Often the value of correlations established with systems capable of exhibiting geometrical isomerism has been reduced by examination of only some of the possible isomers.

The substances listed in Table 1 were therefore synthesised (preceding paper), rigorously purified, and examined under similar conditions: they represent a complete set of variations on two related structural themes. Correlations deduced from these results were supported by data from a wider range of compounds shown in Tables 2 and 3. In a separate study the spectra of allylic and progargylic halides (Table 4) were investigated.

Spectroscopic Work and Explanation of Tables 1—4.—Although the compounds in Table 1 were examined fairly recently, the remaining spectra were obtained during the last three years. This wide separation in time, and the fact that the main function of each determination was to facilitate contemporaneous research, account for the diversity of conditions used.

The spectra were recorded on a Perkin–Elmer model 21 double-beam spectrometer fitted with a sodium chloride prism. The condition specified at the heads of the columns of the Tables is that pertaining to the majority of cases for a particular band. Exceptions are indicated by the superscripts: * = Nujol, † = CCl_4, ‡ = CS_2, § = liquid, ‖ = melt.

Where possible quantitative intensity values are given. These data are apparent extinction coefficients (ε) calculated in the usual way (Henbest, Meakins, and Wood, *J.*, 1954, 800). [With some of the bands, maximal absorption was not within the range (*ca.* 40—70%) generally considered most suitable for quantitative treatment. Thus in extreme cases the intensity values may be in error by factors as large as 1·5.] Elsewhere the usual terms (s = strong, m = medium, w = weak) are used. The two systems are connected by the approximate relations: w = ε, 35—70; m = ε, 70—150; s = $\varepsilon > 150$.

Frequencies are in cm.$^{-1}$, and the maximal errors, for sharp bands, are estimated as ±15, ±8, and ±5 cm.$^{-1}$ at 2300, 1700, and 900 cm.$^{-1}$, respectively. In the Tables the frequency of a band is followed by an intensity description.

Under the conditions used, the acids existed wholly *§‖ or mainly †‡ in the dimeric form, and the bands quoted refer to this state. With solutions, weaker bands due to the monomers (*e.g.* C=O stretching ~1750 cm.$^{-1}$) were observed, but these have not been listed.

The meanings of other terms used are: sh = shoulder on a neighbouring (main) band,

* Part XLIX, preceding paper.

— = no appreciable band ($\varepsilon > 40$) in the frequency range indicated, ni = frequency range not investigated, [ ] = " accidental band," *i.e.*, that a band does occur in the frequency range, but that it is not considered to be due to the vibration specified at the head of the column, ? = assignment indicated is doubtful, *c* and *t* = *cis* and *trans*, respectively.

The references in the Tables are :

a, unpublished work from these laboratories. b, Bates, Jones, and Whiting, *J.*, 1954, 1854. c, Nayler and Whiting, *J.*, in the press. d, Kuhn and Grundmann, *Ber.*, 1936, **69**, 1757. e, Nayler and Whiting, *J.*, 1954, 4006. f, Nayler, Jones, and Whiting, forthcoming publication. g, Allan and Whiting, *J.*, 1953, 3314. h, Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583. i, Preceding paper. j, Shaw and Whiting, *J.*, 1954, 3217. k, Marshall and Whiting, forthcoming publication. l, Heilbron, Sondheimer, and Jones, *J.*, 1947, 1586. m, Jones, Shaw, and Whiting, *J.*, 1954, 3212. n, Favorski and Sakara, *J. Russ. Phys. Chem. Soc.*, 1918, **50**, 43. o, Jones and Whiting, *J.*, 1949, 1423. p, Jones, Mansfield, and Whiting, *J.*, 1954, 3208. q, Jones, Thompson, and Whiting, forthcoming publication. r, Bu'Lock, Jones, Mansfield, Thompson, and Whiting, *Chem. and Ind.*, 1954, 990. s, Johnson, *J.*, 1946, 1009. t, Cook, Jones, and Whiting, *J.*, 1952, 2883.

C≡C *Stretching*.—In unconjugated acetylenes this vibration gives weak bands in the 2300—2100 cm.$^{-1}$ region (Wotiz and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 3441; Wotiz, Miller, and Palchak, *ibid.*, 1950, **72**, 5055). Conjugation with olefinic, or other acetylenic, bonds causes some intensification and (usually) a decrease in frequency, but these changes are much smaller than those observed in the C=C stretching band of conjugated olefins (see, *inter al.*, Sheppard, *J. Chem. Phys.*, 1949, **17**, 74; Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 3838; 1953, **75**, 1372, 3430, for C≡C stretching : Blout, Fields, and Karplus, *ibid.*, 1948, **70**, 194, for C=C stretching). Thus, it appears that a hydrocarbon must contain four triple bonds in conjugation to give an appreciable C≡C stretching band {cf. Me·[C≡C]$_3$·Me, 2222 w, and Me·[C≡C]$_4$·Me, 2237 m (Cook, Jones, and Whiting, *J.*, 1952, 2883)}.

There does not appear to have been any systematic study of the effect of conjugation with carboxy- or methoxycarbonyl groups. The data in Tables 1 and 3 show that such conjugation causes the expected, marked intensification of the C≡C stretching absorption. The results can be summarised : C≡C stretching in ·[C≡C]$_n$·CO$_2$R ; R = H or Me, n = 1, medium band 2260—2235 cm.$^{-1}$, n = 2 or 3, strong band(s) 2270—2200 cm.$^{-1}$.

For n = 1 the frequency range is small; the exception (compound 70) would be expected to absorb at lower frequency. In the cases with n = 2 or 3 the band is split into two components (compounds 23, 24, and 81—87) presumably by mechanical coupling among the vibrations of the triple bonds. The higher-frequency band is generally the more intense in solution spectra, but we have often observed a reversal of this relation when using solid films or Nujol suspensions. It is remarkable that the frequency ranges are, in both cases, above rather than below the position (*ca.* 2200 cm.$^{-1}$) associated with the unconjugated disubstituted acetylenes.

Comparison of compounds 13—16 with 17—20 shows that the C≡C band is weaker in the former group, apparently because the usual polarising influence of the CO$_2$R residue is here attenuated by the interposition of an ethylenic linkage. In compounds 72 and 73 the triple-bond vibration is centrosymmetric, and is therefore inactive in the infra-red.

C=O *Stretching*.—The figures (Tables 1 and 3), which must be considered separately for acids and esters, illustrate the shift of the band to lower frequency when one C=C or C≡C is in conjugation with CO$_2$R. (The frequencies of corresponding saturated acids and esters are about 1710 and 1740 cm.$^{-1}$, respectively.) There is an indication that a slightly greater decrease in frequency of the C=O stretching is produced by a conjugated triple bond than by a double bond. In other series it is known that as the conjugation is extended the addition of each *olefinic* bond makes progressively less difference to the C=O frequency (Blout *et al.*, *loc. cit.*; R. N. Jones and Dobriner, *Vitamins and Hormones*, 1949, **7**, 293). With the conjugated acetylenic compounds the esters containing one or two triple bonds (nos. 21, 23, 66, 70, 74, 76, 78, and 81) have values close to 1717 cm.$^{-1}$, but when three such bonds are involved (84 and 87) a higher frequency, ~1722 cm.$^{-1}$, is observed. Thus, extending the *acetylenic* conjugation causes first a drop, then a rise in frequency. An explanation of these differences is found by considering the pK values of the acids in the

TABLE 1. *Conjugated esters and acids.*

No.	C≡C stretching (CCl_4)		C=O stretching, esters (CS_2)	C=O stretching, acids (CCl_4)	C=C stretching (CCl_4)		Olefinic CH out-of-plane bending (CS_2), *trans*			Olefinic CH out-of-plane bending (CS_2), *cis*		C≡C·CO_2R (CS_2)
1 Me·CH=CH·CO_2Me	—	—	1726(850)	—	1659(180)	—	969(220)	—	—	—	—	—
2 Me·CH=CH·CO_2H	—	—	—	1694(750)	1651(250) ‡	—	970(350)	—	—	—	[695(55)]	—
3 Me·CH=CH·CO_2Me	—	—	1721(800)	—	1644(120)	—	—	—	—	812(160)	—	—
4 Me·CH=CH·CO_2H	—	—	—	1692(700) ‡	1639(250) ‡	—	—	—	—	818(130)	—	—
5 Me·CH=CH·CH=CH·CO_2Me	—	—	1716(850)	—	1642(200)	1614(100)	995(350)	943(60)	—	—	—	—
6 Me·CH=CH·CH=CH·CO_2H	—	—	—	1702 s *	1639 s *	1613 s *	998 s *	945 w *	—	—	[697 m] *	—
7 Me·CH=CH·CH=CH·CO_2Me	—	—	1715(800)	—	1634(200)	1598 m	990(150)	951(50)	936(30)	—	?687(100)	—
8 Me·CH=CH·CH=CH·CO_2H	—	—	—	1683(1100)	1627(230)	1601(140)	990(170)	949(100)	—	—	?683(110)	—
9 Me·CH=CH·CH=CH·CO_2Me	—	—	1715(700)	—	1639(200)	1597 m	996(200)	958(140)	938(100)	832(180)	—	—
10 Me·CH=CH·CH=CH·CO_2H	—	—	—	1687(450)	1636(200)	1600 m	996(200)	958(300)	—	837(170)	—	—
11 Me·CH=CH·CH=CH·CO_2Me	—	—	1715(650)	—	1623(200)	1587 m	—	—	—	821(180)	?662(130)	—
12 Me·CH=CH·CH=CH·CO_2H	—	—	—	1691s ‖	1620 s ‖	1598 m ‖	—	—	—	829(160)	?662(150)	—
13 Me·C≡C·CH=CH·CO_2Me	2270(70)	—	1719(850)	—	1615(200)	—	959(200)	—	—	—	—	—
14 Me·C≡C·CH=CH·CO_2H	2270(70)	—	—	1685 s	1619 s	—	959(400)	—	—	—	[660(80)]	—
15 Me·C≡C·CH=CH·CO_2Me	2229(80)	—	1733(450) 1718(250)	—	1612(200)	—	—	—	—	812(200)	—	—
16 Me·C≡C·CH=CH·CO_2H	2224(70)	—	—	1702(450)	1609(220)	—	—	—	—	819(160)	—	—
17 Me·CH=CH·C≡C·CO_2Me	2221(140)	—	1708(550)	—	1626(40)	—	948(250)	—	—	—	—	746(160)
18 Me·CH=CH·C≡C·CO_2H	2224 w *	2190 s *	—	1667 s *	1618 w *	—	951 m *	—	—	—	—	756 m *
19 Me·CH=CH·C≡C·CO_2Me	2224(170)	—	1713(500)	—	1615(30)	—	—	—	—	721(120)	—	745(140)
20 Me·CH=CH·C≡C·CO_2H	2219(220)	—	—	1692(450)	1615(45)	—	—	—	—	720(150)	[662(160)]	757(60)
21 Me·C≡C·CO_2Me	2242(150)	—	1718(600)	—	—	—	—	—	—	—	—	748(100)
22 Me·C≡C·CO_2H	2246(200)	2140(20)	—	1684(750) ‡	—	—	—	—	—	—	—	750(70)
23 Me·C≡C·C≡C·CO_2Me	2260(400)	2190(80)	1716(850)	—	—	—	—	—	—	—	—	740(160)
24 Me·C≡C·C≡C·CO_2H	2270(450)	2180(80)	—	1688(800) ‡	—	—	—	—	—	—	[700(95)]	742(80)

TABLE 2. *Miscellaneous ethylenic compounds.*

No.		Olefinic CH out-of-plane bending (CS_2) *trans*			*cis*	$C{\equiv}C{\cdot}CO_2R$ (CS_2)	Refs.
25	Me·CH=CH·CH=CH·CH_2·OH	985(270)	—	928(50)	—	—	
26	HO·CH_2·CH=CH·CH=CH·CH_2·OH	993 s †	958 w †	—	—	—	b
27	Me·CH=CH·CH=CH·CH(OH)·CHMe·OH	988 s †	—	—	—	—	c
28	HO_2C·CH_2·CH=CH·CH=CH·CH_2·CO_2H	989 s *	937 m *	—	—	—	d
29	$[CH_2]_5$>C(OH)·CH=CH·CH=CH·C(OH)<$[CH_2]_5$	990 s †	958 m †	—	—	—	b
30	Me·[CH=CH]$_2$·CH(OH)·C≡C·CH(OH)·[CH=CH]$_2$·Me (all *trans*)	993 s *	—	923 m *	—	—	c
31	{Me·[CH=CH]$_2$·CH(OH)·C≡}$_2$ (all *trans*)	1006 s *	964 m *	925 w *	—	—	c
32	CH_2=CMe·CH=CH·CH=CMe·CH=CH_2	—	959 s †	—	—	—	e
33	CH_2=CMe·CH=CH·CMe=CH_2	—	959 s †	—	—	—	f
34	Me·CH=CH·C≡CH	—	956(140)	—	—	—	g
35	Me·CH=CH·C≡CH	—	[958(50)]	—	723(115)	—	g
36	Me·CH=CH·C≡C·C≡C·CH=CHMe	—	945(300)	—	—	—	a
37	Me·CH=CH·C≡C·C≡C·CH=CHMe	—	—	—	716(320)	—	a
38	Me·CH=CH·C≡C·CH_2·OH	—	953(130)	—	—	—	a
39	Me·CH=CH·C≡C·CH_2·OH	—	—	—	718(150)	—	a
40	HO·CH_2·CH_2·CH=CH·C≡C·CH_2·CH_2·OH	—	957 s †	—	—	—	a
41	Me·CH=CH·C≡C·CH_2Cl	—	951(190)	—	—	—	a
42	Me·CH=CH·C≡C·CH_2Cl	—	—	—	717(160)	—	a
43	Me·CH=CH·C≡C·CH_2·CO_2H	—	950(170)	—	—	—	a
44	HC≡C·CH=CH·CH_2·OH	—	952(130)	—	—	—	h
45	HC≡C·CH=CH·CHMe·OH	—	956(145)	—	—	—	a
46	HC≡C·CH=CH·CHMe·OH	—	—	—	756(65)	—	a
47	Me·C≡C·CH=CH·CH_2·OH (mainly *trans*)	—	953(130)	—	—	—	i
48	HC≡C·CH=CH·CH_2Cl	—	950(150)	—	—	—	a
49	Me·C≡C·CH=CH·CH_2Cl (*cis-trans* mixture)	—	950(140)	—	764(25)	—	a
50	Bu^n·C≡C·CH=CH·CH_2Cl (mainly *trans*)	—	952(120)	—	—	—	a
51	HC≡C·CH=CH·CHMeCl	—	948(175)	—	—	—	a
52	HC≡C·CH=CH·CHMeCl	—	[948(20)]	—	759(125)	—	a
53	HO·CPh$_2$·CH=CH·C≡C·CH=CH·CPh$_2$·OH	—	958 ms †	—	ni	ni	b
54	(Me·[CH=CH]$_2$·C≡)$_2$ (all *trans*)	978 s †	—	930 m †	ni	ni	a
55	Ph·CH=CH·CH=CH·CO_2H	1004 s *	—	—	—	—	
56	MeO_2C·[CH=CH]$_4$·CO_2Me (all *trans*)	1022 s *	—	—	—	—	j
57	*p*-MeO·C_6H_4·[CH=CH]$_2$·CO_2Me (all *trans*)	1005 s *	—	—	—	—	k
58	*p*-MeO·C_6H_4·[CH=CH]$_3$·CO_2Me (all *trans*)	1010 s *	—	—	—	—	k
59	*p*-MeO·C_6H_4·[CH=CH]$_4$·CO_2Me (all *trans*)	1014 s *	—	—	—	—	k
60	HC≡C·CH=CH·CO_2H	—	958 s	—	[685 m]	—	e
61	MeO_2C·[C≡C]$_2$·CH=CH·CO_2Me	—	956(290)	—	[710(55)]	742(50)	m
62	MeO_2C·[C≡C]$_2$·CH=CH·CO_2H	—	958(120) †	—	ni	ni	m
63	MeO_2C·C≡C·CH=CH·CH=CH·CO_2Me	991 s	940 w	—	—	742 m	m
64	HO_2C·C≡C·CH=CH·CH=CH·CO_2H	1000 s *	950 w *	—	—	747 m ‖	m
65	MeO_2C·C≡C·CH=CH·CH=CH·CO_2Me	990 s	955 w	—	822 m	745 m	m

TABLE 3. *Conjugated acetylenic esters and acids.*

No.		C≡C stretching (CCl_4)			C=O stretching (CCl_4) esters	acids	C≡C·CO_2R (CS_2)	Refs.
66	HC≡C·CO_2Me	ni	—	—	1719 s‡	—	750(150)	
67	Et·C≡C·CO_2H	2258 m	—	—	—	1690 s	ni	
68	Bu^t·CH_2·C≡C·CO_2H	2250 m‡	—	—	—	1685 s‡	751(60)	n
69	Ph·CH_2·CH_2·C≡C·CO_2H	2250 m	—	—	—	1693 s	ni	a
70	$[CH_2]_5$>C(OH)·C≡C·CO_2Me	2208 m‡	—	—	1715 s	—	747(120)	o
71	HO_2C·CH_2·CH_2·C≡C·CO_2H	2250 m*	—	—	—	1695 s*	744 w*	p
72	MeO_2C·C≡C·CO_2Me	—	—	—	1722 s§	—	749 m§	
73	HO_2C·C≡C·CO_2H	—	—	—	—	1700 s*	745 m*	
74	HC≡C·CH_2·CH_2·C≡C·CO_2Me	2242(135)	—	—	1715 s	—	ni	j
75	HC≡C·CH_2·CH_2·C≡C·CO_2H	2248(190)	2215 Sh	—	—	1693 s	ni	j
76	$(MeO_2C·C≡C·CH_2·)_2$	2252(185)	—	—	1717 s	—	ni	m
77	$(HO_2C·C≡C·CH_2·)_2$	2245 s*	—	—	—	1680 s*	750 m*	m
78	$(MeO_2C·C≡C·CH_2·CH_2)_2$	2242(220)	—	—	1717 s	—	ni	m
79	$(HO_2C·C≡C·CH_2·CH_2)_2$	2236 s*	—	—	—	1680 s*	752 m*	m
80	Ph·C≡C·CO_2Me	ni	—	—	ni	—	747 Sh (on 755 Ph)	
81	Et·$[C≡C]_2$·CO_2Me	2243 s§	2187 Sh§	2160 m§	1717 s§	—	745 m§	q
82	Et·$[C≡C]_2$·CO_2H	2240 s*	2195 Sh*	2160 m*	—	1680 s*	743 m*	q
83	Bu^n·$[C≡C]_2$·CO_2H	2252 s	2170 m	—	—	1693 s	742(55)	q
84	Me·$[C≡C]_3$·CO_2Me	2210 s	2125 m	—	1721 s	—	740(135)	r
85	Me·$[C≡C]_3$·CO_2H	2210 s	2135 w	—	—	1694 s	ni	r
86	Et·$[C≡C]_3$·CO_2H	2200 s	2130 m	—	—	1684 s	ni	q
87	HO·CH_2·$[C≡C]_3$·CO_2Me	2220 s	2133 w	—	1724 s	—	ni	r

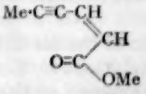
TABLE 4. *Allylic and propargylic halides.*

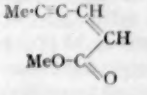
No.		C=C·C·Hal and C≡C·C·Hal(CS_2)					Refs.
48	HC≡C·CH=CH·CH_2Cl (*t*)	1244(75)	—	—	691(75)	—	a
49	Me·C≡C·CH=CH·CH_2Cl (*cis-trans* mixture)	1246(80)	—	—	681(70)	—	a
50	Bu^n·C≡C·CH=CH·CH_2Cl (mainly *trans*)	1250(60)	1244(75)	—	680(60)	—	a
41	Me·CH=CH·C≡C·CH_2Cl (*t*)	1260(200)	—	—	693(200)	—	a
42	Me·CH=CH·C≡C·CH_2Cl (*c*)	1260(200)	—	—	693(200)	—	a
88	Me·C≡C·CH_2Cl	1260(140)	—	—	702(75)	688(90)	
89	$ClCH_2$·C≡C·CH_2Cl	1262 s§	—	—	699 s§	—	s
90	Me·CHCl·$[C≡C]_2$·CH_2Cl	1269 s§	1243 s§	1220 s§	700 s	—	q
91	Et·CHCl·$[C≡C]_2$·CH_2Cl	1267 s§	1256 s§	—	700 s§	—	q
92	$ClCH_2$·$[C≡C]_2$·CH_2Cl	1254 s§	—	—	699 s§	—	t
93	$ClCH_2$·$[C≡C]_4$·CH_2Cl	1261 s	—	—	721 m	703 m	t
94	Me·C≡C·CH_2Br	1221 s§	1211 s§	—	—	—	
95	Bu^n·C≡C·CHMeBr	1184(145)	—	—	—	—	a
96	Me·C≡C·CH_2I	1180 s§	1146 s§	—	—	—	
97	Bu^n·C≡C·CH_2I	1172 s§	1143 s§	—	—	—	

two series. In the olefinic compounds the pK value is not appreciably affected by conjugation, and this factor is not involved in determining the C=O values. However, the strength of the acetylenic acids increases with the number of conjugated triple bonds (Jones, Mansfield, and Whiting, forthcoming publication). This would indicate increased bond order of the C=O in the acids, and presumably a similar effect operates in the derived esters. Some analogy is found in the relations between pK and the OH and CO stretching frequencies of acids (Goulden, *Spectrochim. Acta*, 1954, **6**, 129; Flett, *Trans. Faraday Soc.*, 1948, **44**, 767).

The intensity of the C=O band in the esters (Table 1) varies slightly with the nature of the unsaturated bond, diminishing in the order *trans* > *cis* > acetylenic. Compound 15 is most unusual in that the spectrum of its solution shows two C=O bands. The occurrence of two stretching bands from one C=O group implies the existence of two different " states " for the C=O group. Such states generally arise through differences in the type or degree of hydrogen bonding operating in them (R. N. Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820), and doubling in the spectra of solid materials is quite

common (see, *e.g.*, Zürcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562). A second cause is exemplified with 2-bromo*cyclo*hexanone (Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301), where the two states are those having different conformations of the bromine atom. The extent of dipolar interaction differs in the two, with consequential separation of the C=O frequencies. An explanation along these lines can be employed with compound 15, the two forms being the rotational isomers (I) and (II). In the absence of dipolar interaction the frequency separation of the C=O bands of (I) and (II) would be small (cf. Short, *J.*, 1952, 206). However, the C–C≡C and C=O dipoles will be almost parallel, and nearly perpendicular, to each other in (I) and (II) respectively. Thus the large frequency separation, 15 cm.$^{-1}$, might reasonably be expected.*


(I)


(II)

C≡C *Stretching*.—The spectra of compounds 1—20 show the expected numbers of C≡C bands, two in nos. 5—12, one in the rest. The operation of a geometric effect is apparent (see, *inter al.*, Sinclair, McKay, Myers, and R. N. Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 2578). The conversion of either the αβ- or the γδ-ethylenic bond from *trans* into *cis* causes a shift of the band to lower frequency. Thus, the stereochemistry influences the *intensity* of the C=O stretching band, and the *frequency* of the C=C stretching band : no such regularities are found in the complementary properties.

Compounds 17—20 absorb strongly in this region, whereas 13—16 have only weak bands : this is the converse of their behaviour in the C≡C range. The relative intensities of the C=C and C≡C bands clearly indicate which linkage is adjacent to the CO_2R group.

Olefinic C–H *Out-of-plane Bending*.—While the 1 : 2-disubstituted *trans*-olefinic system

TABLE 5. *Out-of-plane bending frequencies of conjugated* trans- *and* cis-*bonds.*

trans		Refs.	*cis*		Refs.
(CH=CH	965 s	u	CH=CH	~700 m, variable	u, v
CH=CH·CH=CH	990 s	w, x, ii	—	—	
•CH=CH·CH=CH	985 s, 950 m	w, y	—	—	
CH=CH·CH=CH·CH=CH	997 s	x, z, cc, ii	—	—	
CH=CH·CH=CH·CH=CH	990 s, 965 m	x, z, cc	—	—	
[CH=CH]$_n$ ($n > 3$)	increases with n; upper limit ~1000 s	x, aa, ii	—	—	
CH=CH·CO·X (X = OH, OR, NHR)	980 s	bb, dd, ee, ff, ii	CH=CH·CO·X (X = (OH, OR, NHR)	820 s	bb, dd, ii
CH=CH·C≡C	950 s	w, gg, hh, ii	CH=CH·C≡C	720 s	ii

* Ref. w gives a third band (1020) for this system. It is probable, however, that this band is associated with the ester group present in the compounds studied (cf. Sinclair, McKay, and R. N. Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 2570).

u, Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1. v, Henbest *et al.*, *loc. cit.* w, Celmer *et al.*, *loc. cit.* x, Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433. y, Jackson, Paschke, Tolberg, Boyd, and Wheeler, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 229. z, Bickford, Du Pré, Mack, and O'Connor, *ibid.*, 1953, **30**, 376. aa, Woods and Schwartzman, *J. Amer. Chem. Soc.*, 1949, **71**, 1396. bb, Crombie, *J.*, 1952, 2997, 4338. cc, Crombie and Taylor, *J.*, 1954, 2816. dd, Sinclair *et al.*, *loc. cit.*, p. 2578. ee, Kitson, *Analyt. Chem.*, 1953, **25**, 1470. ff, Freeman, *J. Amer. Chem. Soc.*, 1953, **75**, 1859. gg, Ahlers and Ligthelm, *J.*, 1952, 5039. hh, Gunstone and McGee, *Chem. and Ind.*, 1954, 1112. ii, this paper.

* Since this paper was prepared, it has been possible, through the courtesy of Professor N. A. Sörensen, to examine the infrared spectra of the naturally-occurring methyl deca-*cis*-2-ene-4 : 6-diynoate and methyl deca-*cis*-2 : 8-diene-4 : 6-diynoate. Both show double carbonyl bands at 1730 and 1717 cm.$^{-1}$ which are evidently characteristic of the grouping *cis*-R·C≡C·CH=CH·CO_2Me. Both also absorbed strongly at 813 cm.$^{-1}$ (*cis*-CH=CH·CO_2Me), and the latter only showed a strong band at 713 cm.$^{-1}$ (*cis*-Me·CH=CH·C≡C).

can be readily detected by the out-of-plane bending vibration, use of the corresponding band for the *cis*-bond has been regarded as less satisfactory (Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 42). The frequency of the *cis*-band is certainly more variable than that of the *trans* (Henbest *et al.*, *loc. cit.*), but this variability should actually enhance its value once the necessary correlations have been established.

The information available about the bands of conjugated ethylenic bonds is summarised in Table 5. Average frequencies, rather than frequency ranges, are given in view of the small numbers of examples of each type. [A few representatives of other systems, *e.g.*, the *cis-cis-trans*-conjugated trienes (Ahlers and Dennison, *Chem. and Ind.*, 1954, 603; Ahlers, Dennison and O'Neill, *Nature*, 1954, **173**, 1045) have been studied, but no generalisations are possible in these cases.]

Strong bands at 820 cm.$^{-1}$ (Table 1) are characteristic of the *cis*-CH=CH·CO·X system, and are of obvious diagnostic value. The tentative correlations by Sinclair *et al.* (*loc. cit.*) and by Crombie (*locc. cit.*) are thus confirmed. (The presence of this band was used in assigning the bond configurations in compound 65.) The shift (*ca.* 100 cm.$^{-1}$) in passing from simple *cis*-olefins to conjugated *cis*-olefinic acids and their derivatives is much bigger than that (*ca.* 15 cm.$^{-1}$) found with *trans*-systems. A comparable shift (*ca.* 60 cm.$^{-1}$) was, however, observed by Freeman (*loc. cit.*) in the α-methylidene acids.

Conjugation of the *trans*-CH=CH bond with a CO·X group increases the bending frequency. Compounds 1 and 2, the simplest members of the series, show a smaller shift than is usual. Conjugation with other *trans*-bonds or with vinyl groups (Rasmussen and Brattain, *J. Chem. Phys.*, 1947, **15**, 131; refs. w, x, and aa of Table 5) also increases the frequency of this band. Conjugation with tri- or tetra-substituted olefinic bonds (Inhoffen, Brückner, Gründel, and Quinkert, *Ber.*, 1954, **87**, 1407) or with CH_2=CMe· and ·CH=CMe groupings (compounds 32 and 33) produces a small displacement to *lower* frequency.

Acetylenic conjugation moves the *trans*-band to lower frequency (compounds 34, 36, 38, 40, 41, 43, and 54). The compounds containing the *cis*-Me·CH=CH·C≡C· unit absorb fairly consistently at 720 cm.$^{-1}$ (compounds 35, 37, 39, and 42). The stability of the *trans*-band towards α-substitution (·C≡C·CH=CH·CX, X = Cl or OH; compounds 44, 45, and 47—51) contrasts with the behaviour of the *cis*-band (nos. 46, 49, and 52) in which a displacement to higher frequency is produced (cf. Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1950, **72**, 727; Mislow and Hellman, *ibid.*, 1951, **73**, 244).

In the remaining compounds of Table 2, and in compounds 5—20 of Table 1, the conjugated system contains at least three multiple bonds. Two effects will influence the bending frequencies, and the results are interpreted in terms of the tendencies already discussed. In some cases the effects will act in the same direction: thus in compound 5 (Table 1) the system *trans-trans*-C=C·C=C·CO_2Me is regarded as *trans-trans*-C=C·C=C plus *trans*-C=C·CO_2Me, and the observed value (995) accords well with shifts to higher frequency of both the diene and ester components. With other systems (*e.g.*, compound 60; *trans*-C≡C·C=C·CO_2Me divided into *trans*-C≡C·C=C and *trans*-C=C·CO_2Me) the factors are opposed, and the net effect is small. In related pairs of acids and esters (*e.g.*, 1 and 2, 13 and 14) the former usually have the stronger *trans*-band. This is caused by the contribution at the ethylenic frequency of the acidic hydroxyl out-of-plane bending vibration (a broad band centred around 930 cm.$^{-1}$).

It was not possible to identify the bending bands of the *γδ-cis*-bonds in compounds 7, 8, 11, and 12. Tentative assignments are given in Table 1, but their value is somewhat decreased by the occurrence of similar bands in the spectra of some of the acids lacking a *cis*-bond.

Band Characteristic of C≡C·CO_2R (R = H, Me).—These compounds are listed in Tables 3, 1 (nos. 17—24), and 2 (nos. 62—65). The thirteen esters examined have a medium band in the 750—740 cm.$^{-1}$ range, while the acids show a weaker band between 757 and 742 cm.$^{-1}$. These useful bands appear to be characteristic of conjugated acetylenic acids and esters—they do not occur in the spectra of the corresponding olefinic compounds. The vibrational assignments are not known. With saturated acids a band in the range 700—575 cm.$^{-1}$ has been correlated with a skeletal deformation involving the O–C=O angle of the acid dimer (Hadzi

and Sheppard, *Proc. Roy. Soc.*, **1953**, *A*, **216**, 247). Such an assignment could be applied to the acetylenic acids, but in the (monomeric) esters the frequency of the corresponding vibration would be appreciably different.

Allylic and Propargylic Halides.—Previous work on propargylic halides (Wotiz *et al.*, *locc. cit.*; Jacobs and Brill, *J. Amer. Chem. Soc.*, 1953, **75**, 1314; Hatch and Kidwell, *ibid.*, 1954, **76**, 289) has been confined to the C≡C stretching vibration, and to the presence or absence of bands in the 1700 cm.$^{-1}$ region.

The results in Table 4 show that both the systems C≡C·CH_2Cl and CH=CH·CH_2Cl give two bands, near 1255 and 700 cm.$^{-1}$, which are strong in the propargylic chlorides and of medium intensity in the allylic chlorides. In some cases (88, 90, 91, and 93) splitting of either the higher- or the lower-frequency band occurs. With the propargylic bromides and iodides the higher band moves to lower frequency, and the lower one disappears, presumably by displacement to below 650 cm.$^{-1}$, the end of the sodium chloride range. These findings parallel those of Kitson (*loc. cit.*) who observed the higher-frequency band in both series, and reported frequencies for the allylic chlorides, bromides, and iodides of 1248, 1204, and 1150 cm.$^{-1}$, respectively.

The band near 700 cm.$^{-1}$ in the chlorides is probably due to C–Cl stretching: the absence of corresponding bands above 650 cm.$^{-1}$ in the bromides and iodides supports this suggestion. For the higher-frequency band there is no obvious assignment. None of the compounds in Table 4 showed selective absorption around 1700 cm.$^{-1}$ (cf. Wotiz *et al.*, *locc. cit.*).

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Perfluoroalkyl Derivatives of Nitrogen. Part I. Perfluoro-2-methyl-1 : 2-oxazetidine and Perfluoro(alkylenealkylamines).*

By D. A. BARR and R. N. HASZELDINE.

[Reprint Order No. 6086.]

Trifluoronitrosomethane reacts quantitatively with tetrafluoroethylene to give perfluoro-2-methyl-1 : 2-oxazetidine (I) and a polymer of formula [·N(CF_3)·O·CF_2·CF_2·]$_n$ and molecular weight >7000. Pyrolysis of the oxazetidine or of the polymer gives, quantitatively, equimolar amounts of perfluoro(methylenemethylamine), CF_3·N:CF_2, and carbonyl fluoride. Chemical, physical, and spectroscopic properties are reported for these new compounds. Improved techniques are described for the preparation of trifluoronitrosomethane.

TRIFLUORONITROSOMETHANE, a deep-blue monomeric gas first prepared by Ruff and Giese (*Ber.*, 1936, **69**, 598, 684) by treatment of a silver cyanide–silver nitrate mixture with fluorine, was subsequently prepared in good yield by the interaction of trifluoroiodomethane and nitric oxide, and its properties were studied.* It is extremely reactive and can readily be converted into trifluoronitromethane, hexafluoroazoxymethane, and an orange dimer which has structure (CF_2)(CF_3·O)N·NO or (CF_3)$_2$N·O·NO. The present communication describes improved techniques for the preparation of trifluoronitrosomethane and similar nitroso-compounds, and its conversion into perfluoro-2-methyl-1 : 2-oxazetidine (I) and perfluoro(methylenemethylamine) (V).

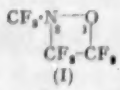
The only disadvantage of the initial preparative method for trifluoronitrosomethane from trifluoroiodomethane and nitric oxide was that sealed tubes or silica reaction flasks were necessary, so that several small-scale experiments were required to obtain substantial quantities of the gas. A simple apparatus has now been developed (see Fig. 1) which

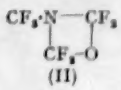
* For earlier work on perfluoroalkyl derivatives of nitrogen see Haszeldine, *Nature*, **1951**, **168**, 1028; *J.*, 1953, 2075; Haszeldine and Jander, *J.*, **1953**, 4172; 1954, 696, 912, 919; *Naturwiss.*, **1953**, **40**, 579.

avoids the use of pressure, is constructed of readily available Pyrex apparatus, yet gives yields as high as those obtained earlier, and in which up to 0·25 mole of trifluoroiodomethane can be used per experiment. These improvements make the pure nitroso-compound readily available.

Trifluoronitrosomethane, as reported earlier, is stable as a gas at room temperature or as a liquid under pressure. Banus (*J.*, **1953**, 3755) confirmed the synthesis of the nitroso-compound, but stated that it decomposes spontaneously at room temperature, particularly in the gas phase or when shaken with mercury; this is completely fallacious. The original observations have again been confirmed, and in clean apparatus the nitroso-compound is quite stable to water, to storage, or to shaking with mercury, whereas moist soda-glass surfaces, bases, or light rapidly bring about decomposition. Unless these precautions are taken, therefore, decomposition products soon contaminate the nitroso-compound and cause the difficulties reported by Banus; with these precautions the purification procedure is simple (see p. 1886).

Trifluoronitrosomethane combines slowly and quantitatively with tetrafluoroethylene in the dark at room temperature to give 30—65% of a colourless gas (b. p. −6·8°) and 35—70% of an almost colourless viscous oil. The ratio of gas to oil can be controlled by choice of reaction temperature; higher temperatures favour the former. The gas has molecular formula C_3ONF_7, and is unaffected by water, aqueous alkali or acid, or ultraviolet light. Possible constitutions are (I)—(IV). Heptafluoronitrosopropane (III) can be eliminated since this is known (*J.*, **1953**, 2075), and is a deep blue gas showing the very characteristic N:O stretching vibration (6·23 μ) in its infrared spectrum. Compound (II) would be colourless, but its formation would require fission of the C–C bond in tetra-


(I)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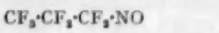
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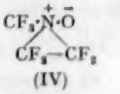
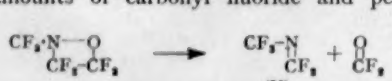

(IV)

fluoroethylene and of the N–O bond in trifluoronitrosomethane and is thus improbable. Perfluoroamine oxides have not yet been prepared; (IV) would certainly be colourless, however, and, since the compound $(CF_3)_3\overset{+}{P}\overset{-}{O}$ (b. p. 23·5°) boils at only a slightly higher temperature than tristrifluoromethylphosphine (b. p. 17°), it might well be volatile [cf. $(CF_3)_3N$, b. p. −6·5°; Haszeldine, *J.*, 1951, 102]. The P–O stretching vibration in the infrared is at the remarkably low wavelength of 7·53 μ for tristrifluoromethylphosphine oxide (Emeléus, Haszeldine, and Paul, *J.*, 1955, 563), so it might be possible for the nitrogen–oxygen vibration in the compound (IV) to lie below the carbon–fluorine stretching vibrations at 8—9 μ. The infrared spectrum of C_3ONF_7 (C.S. No. 210 *) shows no band in the N:O region, although there is a band at 7·05 μ which might be assigned to the $\overset{+}{N}–\overset{-}{O}$ vibration in (IV) (cf. N:O in CF_3·NO, 6·25 μ). It is unlikely that a three-membered ring of the type in (IV) would be stable, however, or that the co-ordinate $\overset{+}{N}–\overset{-}{O}$ bond could be sufficiently non-polar to account for the low b. p. of −6·8°; perfluoro-amines such as $N(CF_3)_3$ are unable to form amine oxides on account of the markedly decreased availability of the lone pair of electrons on the nitrogen atom. The very weak general absorption of C_3ONF_7 in the ultraviolet, the method used for its synthesis, its physical properties, and its infrared spectrum are all consistent with its alternative formulation as perfluoro-2-methyl-1 : 2-oxazetidine (I). Strong support for this is given by its pyrolysis at 550° at low pressure in absence of air to yield twice the original volume of gas, shown to consist of equimolar amounts of carbonyl fluoride and perfluoro(methylenemethylamine) (V);


(V)

* Spectra thus designated have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained on application, quoting the C.S. no., to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

Perfluoro(methylenemethylamine) is a colourless gas whose b. p. (−33·7°) is close to that of hexafluoropropene (−29°); as noted earlier for perfluoro-*tert.*-amines, replacement of a >CF– group in a fluorocarbon by a nitrogen atom scarcely affects the b. p. [cf. $(CF_3)_3N$, b. p. −6·5°; *n*-C_4F_{10}, b. p. −0·5°; Haszeldine, *J.*, 1951, 102]. Its infrared spectrum (C.S. No. 211) shows a strong band at 5·53 μ assigned to the N:C stretching vibration (cf. C:C in $CF_2{\cdot}CF{:}CF_2$, 5·56 μ; Haszeldine, *J.*, 1952, 4259). Homologues of perfluoro(methylenemethylamine) have been obtained recently by pyrolysis of perfluoro-*tert.*-amines (Pearlson and Hals, U.S.P. 2,643,267; *Chem. Abs.*, 1954, **48**, 6461).

Ingold and Weaver (*J.*, 1924, **125**, 1456) obtained compounds formulated as "dimethyleneoxamines" (*i.e.*, as oxazetidines) by the reaction between nitrosobenzene and compounds such as 1 : 1-diphenylethylene or diethyl methylenemalonate [*i.e.*, (i) $Ph_2\overset{\frown}{C{\cdot}CH_2{\cdot}O{\cdot}}\overset{\frown}{NPh}$ and (ii) $(EtO_2C)_2\overset{\frown}{C{\cdot}CH_2{\cdot}NPh{\cdot}O}$]. Staudinger and Jelagin (*Ber.*, 1911, **44**, 365) prepared related compounds from nitrosobenzene and ketens [*e.g.*, $Ph_2C{:}C{:}O + Ph{\cdot}NO \longrightarrow Ph_2\overset{\frown}{C{\cdot}CO{\cdot}NPh{\cdot}O}$ (iii)]. No yields were given for any of the above compounds, but analytical data were obtained. Proof of structure was given by pyrolysis at 170°: (i) afforded $Ph_2C{:}NPh + CH_2O$; (ii) gave $(EtO_2C)_2C{:}C{:}NPh \longrightarrow (EtO_2C)_2CH{\cdot}CO{\cdot}NHPh$ and (iii) gave $Ph_2CO + Ph{\cdot}NCO$; yields were given only for the last reaction, and were then good. The compound (iii) was cleaved by anhydrous hydrogen chloride to give $Ph_2CCl{\cdot}CO{\cdot}NPh{\cdot}OH$. By contrast, perfluoro-2-methyl-1 : 2-oxazetidine is stable to anhydrous hydrogen chloride and to concentrated aqueous acid.

The lower members of the aliphatic azomethines are believed to be cyclic trimers from molecular-weight and vapour-density determinations (Henry, *Compt. rend.*, 1895, **120**, 839; Thomas, *ibid.*, p. 451); they are hydrolysed to the amine and the aldehyde by dilute acids or aqueous bases, and when treated with ethanolic sodium ethoxide yield both the parent amine and, by reduction, the secondary amine (*e.g.*, $Bu^nN{:}CH_2 \longrightarrow Bu^n{\cdot}NH_2 + Bu^n{\cdot}NHMe$) (Henry, *Bull. Acad. roy. Belg.*, 1895, **29**, 26; Franchimont and Van Epps, *Rec. Trav. chim.*, 1896, **15**, 169).

Perfluoro(methylenemethylamine) is rapidly and quantitatively hydrolysed by water to give carbon dioxide, ammonium fluoride, and hydrogen fluoride:

$$CF_2{\cdot}N{:}CF_2 \xrightarrow{H_2O} CF_2{\cdot}NH_2 + COF_2$$

$$CF_2{\cdot}N{:}CF_2 \xrightarrow{-HF} CF_2{:}NH \qquad COF_2 \xrightarrow{H_2O} CO_2 + 2HF$$

$$CF_2{:}NH \xrightarrow{H_2O} COF_2 + NH_3 \xrightarrow{H_2O} CO_2 + NH_4F + HF$$

$$CF_2{:}NH \xrightarrow{H_2O} CF_2(OH){\cdot}NH_2 \xrightarrow{-HF} F{\cdot}CO{\cdot}NH_2 \xrightarrow{H_2O} CO_2 + NH_4F$$

Attempts to prepare the still-unknown trifluoromethylamine, $CF_3{\cdot}NH_2$, by the reaction of perfluoro(methylenemethylamine) with a deficit of water ($CF_3{\cdot}N{:}CF_2 + H_2O \longrightarrow CF_3{\cdot}NH_2 + COF_2$) were unsuccessful. Unchanged perfluoro(methylenemethylamine) and breakdown compounds [silicon tetrafluoride (from reaction of hydrogen fluoride with the reaction vessel) and carbonyl fluoride] were the main products, and infrared spectroscopic examination failed to detect more than traces of gaseous compounds containing N–H bonds. Small amounts of a volatile compound showing absorption in the infrared at 4·4 μ (not carbon dioxide) were always formed under these conditions. Final identification must be deferred, since attempts to isolate the compound failed, but it seems possible that it is cyanogen fluoride produced by the reaction $CF_3{\cdot}NH_2 \longrightarrow FCN + 2HF$, and that the C:N absorption is appearing at 4·4 μ. Trifluoromethyl *iso*cyanate, produced by the reaction

$$CF_3{\cdot}NH_2 + COF_2 \xrightarrow{-HF} CF_3{\cdot}NH{\cdot}COF \xrightarrow{-HF} CF_3{\cdot}NCO$$

is also possible, since the N:C:O vibration would be expected to appear near 4·4 μ. The same unknown product is produced when perfluoro(methylenemethylamine) is heated in

silica, and the formation of cyanogen fluoride or of trifluoromethyl *iso*cyanate (*e.g.*, $CF_2{\cdot}N{:}CF_2 \xrightarrow{SiO_2} CF_3{\cdot}N{:}C{:}O$) concurrently with silicon tetrafluoride can be visualised.

Anhydrous methanol reacts rapidly with perfluoro(methylenemethylamine) to yield dimethyl ether, dimethyl carbonate, and ammonium fluoride, but not carbon dioxide. Methanolysis probably occurs as follows:

$$CF_3{\cdot}N{:}CF_2 + 2CH_3{\cdot}OH \longrightarrow CF_3{\cdot}NH_2 + COF_2 + (CH_3)_2O$$
$$COF_2 + 2CH_3{\cdot}OH \longrightarrow (CH_3{\cdot}O)_2CO + 2HF$$
$$2CH_3{\cdot}OH \xrightarrow{HF} (CH_3)_2O + H_2O$$
$$CF_3{\cdot}NH_2 \xrightarrow{-HF} CF_2{:}NH$$
$$CF_2{:}NH + 2CH_3{\cdot}OH \longrightarrow NH_3 + COF_2 + (CH_3)_2O$$

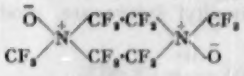
although an alternative mechanism, involving nucleophilic attack on the C:N (cf. the ease of nucleophilic attack on fluoro-olefins such as C_2F_4, C_3F_6), can be visualised:

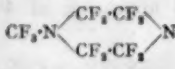
$$CF_3{\cdot}N{:}CF_2 \xrightarrow{MeOH} CF_3{\cdot}NH{\cdot}CF_2{\cdot}OMe \xrightarrow{-HF} CF_2{:}N{\cdot}CF_2{\cdot}OMe \xrightarrow{MeOH} MeO{\cdot}CF_2{\cdot}NH{\cdot}CF_2{\cdot}OMe$$
$$MeO{\cdot}CF_2{\cdot}NH{\cdot}CF_2{\cdot}OMe \xrightarrow[\text{repeated}]{-HF;\ MeOH} (MeO)_2C{\cdot}NH{\cdot}C(OMe)_2 \longrightarrow C(OMe)_4 + NH_3$$
$$C(OMe)_4 \xrightarrow{HF} (CH_3O)_2CO + (CH_3)_2O$$

The colourless viscous oil formed by the reaction of trifluoronitrosomethane with tetrafluoroethylene is insoluble in the common organic solvents. Its infrared spectrum (C.S. No. 212) fails to show the presence of groups such as N:O, NO_2, $N^{+}\!\!\rightarrow\!O^{-}$, ONO, or ONO_2, and N=O, N=N, C=N, and C=C double bonds are absent. The ultraviolet spectrum fails to show specific absorption, again indicating the absence of N:O or NO_2 groups (see *J.*, 1953, 2525; 1954, 691, 912, 919 for infrared and ultraviolet spectra of compounds containing nitrogen and oxygen). The oil has empirical formula C_3ONF_7, *i.e.*, the same as perfluoro-2-methyl-1 : 2-oxazetidine, and this eliminates the possibility that it is a tetrafluoroethylene polymer $(\cdot CF_2{\cdot}CF_2\cdot)_n$, with end groups derived from trifluoronitrosomethane. Two alternatives seemed possible: that the oil was similar to perfluoro-2-methyl-1 : 2-oxazetidine but contained a larger ring system; or that it was an amine oxide. Both of these possibilities were favoured by the analytical data which indicated a 1 : 1 ratio of $CF_3{\cdot}NO : C_2F_4$. The formation of cyclic compounds was possible in the method used, *e.g.*,

$$2CF_3{\cdot}NO + 2C_2F_4 \longrightarrow CF_3{\cdot}N\!\left(\!\begin{array}{l}O{\cdot}CF_2{\cdot}CF_2\\ CF_2{\cdot}CF_2{\cdot}O\end{array}\!\right)N{\cdot}CF_3$$

but this possibility is rejected, since compounds with 8-, 12-, or 16-membered rings would be appreciably volatile (cf. $C_{16}F_{34}$, b. p. 234°), whereas the oil has low volatility (decomposes *in vacuo* about 400° without distillation). A cyclic compound containing more than 20 atoms in the ring would therefore have to be postulated, and it would have to be formed without the concurrent formation of cyclic compounds containing smaller rings, since products intermediate in volatility between perfluoro-2-methyl-1 : 2-oxazetidine and the oil were not present; this is unlikely. The second possibility was more probable, and was examined in detail. An amine oxide such as (VI) would explain the 1 : 1 ratio of $CF_3{\cdot}NO$ to C_2F_4 and the high b. p. could be attributed to the polar nature of the $\overset{+}{N}\!-\!\overset{-}{O}$ bonds; this polarity would also make the nitrogen–oxygen infrared vibration tend towards that for

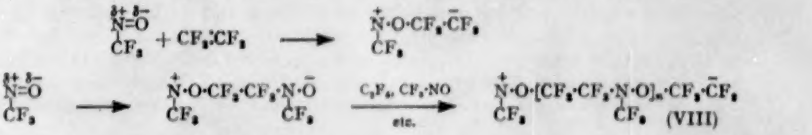
(VI) 

 (VII)

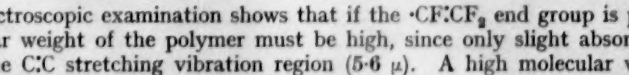
a nitrogen–oxygen single bond and towards that for hydrocarbon amine oxides (8—10·8 μ) so that it would appear in the same region as the carbon–fluorine vibrations, and

make assignment difficult. Attempts were made to reduce the oil to the perfluoro-amine (VII), since it can be predicted with certainty that this amine would be a liquid with about the same volatility as perfluorodimethyl*cyclo*hexane (b. p. 101°) and could be synthesised by fluorination of the corresponding unsubstituted compound. Zinc-dust distillation, sodium amalgam and methanol, zinc and hydrochloric acid, lithium aluminium hydride in ethyl ether, and distillation with sulphur were tried without success. The insolubility of the oil in common solvents rendered use of lithium aluminium hydride difficult. Perfluoromethyl*cyclo*hexane readily dissolves the oil, but even the use of mixtures of this with ethyl ether as solvents for lithium aluminium hydride and the oil failed to cause change in the latter.

A third possibility for the constitution of the oil was therefore considered, namely, that it was a polymer of type (VIII), formed by copolymerisation of tetrafluoroethylene and trifluoronitrosomethane by an ionic mechanism favoured by low temperatures :



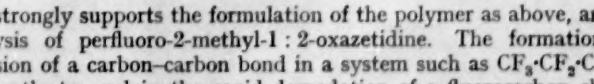
The formation of perfluoro-2-methyl-1 : 2-oxazetidine (I) from the intermediate $CF_3\cdot\overset{+}{N}\cdot O\cdot CF_2\cdot\bar{C}F_2$ is also readily visualised. The facility of nucleophilic attack on tetrafluoroethylene and other polyfluoro-olefins is well established, and the above mechanism, and the fact that formation of the oil occurs preferentially at low temperatures when the reactants are in the liquid phase, are in accord with this. A polymer such as (VIII) thus contains alternate trifluoronitrosomethane and tetrafluoroethylene units, so that the analytical data agree with the empirical formula C_3ONF_7. Chain termination in the polymer might involve disproportionation reactions such as



Infrared spectroscopic examination shows that if the $\cdot CF{:}CF_2$ end group is present at all the molecular weight of the polymer must be high, since only slight absorption can be seen near the C:C stretching vibration region (5·6 μ). A high molecular weight would clearly allow end groups other than those postulated above to be present without marked effect on the analysis of the polymer.

Distinction between (VI) and (VIII) was made on the basis of molecular-weight determination in perfluoromethyl*cyclo*hexane, for which the ebullioscopic constant was determined as 13·0. The mean molecular weight was at least 7000 and possibly much higher [cf. (VI), $M = 398$], and the oil is thus clearly the polymer (VIII).

The polymer is unaffected by hot concentrated sulphuric acid or hot concentrated aqueous potassium hydroxide, but when heated *in vacuo* at 400° in absence of air it yields equimolar amounts of perfluoro(methylenemethylamine) and carbonyl fluoride quantitatively :



This reaction strongly supports the formulation of the polymer as above, and is analogous to the pyrolysis of perfluoro-2-methyl-1 : 2-oxazetidine. The formation of carbonyl fluoride by fission of a carbon–carbon bond in a system such as $CF_3\cdot CF_2\cdot CF_2\cdot O\cdot$ has been postulated recently to explain the rapid degradation of a fluorocarbon chain by photochemical oxidation (Francis and Haszeldine, *J.*, 1955, in the press). Degradation of a fluorocarbon chain containing oxygen by this reaction of carbonyl fluoride elimination will probably prove to be of general application.

Reaction of trifluoronitrosomethane with tetrafluoroethylene followed by pyrolysis

of both the products thus gives perfluoro(methylenemethylamine) quantitatively and extension of the reaction to longer-chain perfluoronitrosoalkanes provides the simplest general route to the compounds $CF_3{\cdot}[CF_2]_n{\cdot}N{:}CF_2$. The reactions of the perfluoro(alkylene-alkylamines), *e.g.*, their reaction with hydrogen fluoride to give bis(perfluoroalkyl)amines such as $(CF_3)_2NH$, will be described in subsequent papers.

Experimental

Preparation and Purification of Trifluoronitrosomethane.—The apparatus is shown in Fig. 1. Into a 20-l. Pyrex flask is fitted, *via* a B24 joint, a clear silica tube *A* sealed at the lower end. A 12″ Hanovia cold mercury lamp (200 v, 15 w), type SNC, which generates mainly 2537 Å radiation, fits loosely inside *A*, whose length is such that the lower end clears by 2—3″ a pool of mercury (400 ml.) inside the flask. The apparatus is evacuated and trifluoroiodomethane (41 g., 0·210 mole) is condensed into the small attached receiver *B*, then, with tap *C* closed, is allowed to expand into the flask. Tap *D* is closed and nitric oxide (12·7 g., 0·422 mole) is condensed into *B* and then allowed to expand into the flask *via D*, which is then closed; the small amount of nitric oxide remaining in *B* is neglected. The flask is mounted on a mechanical shaker which is agitated at such a rate (75 strokes/min.) that the mercury pool swirls up the sides of the flask as shown in Fig. 1, and can thus react readily with any dinitrogen tetroxide

Fig. 1.
Preparation of trifluoronitrosomethane.

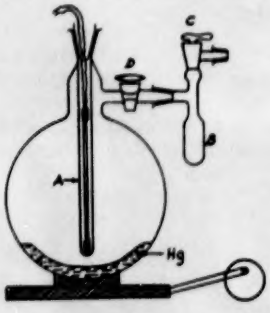
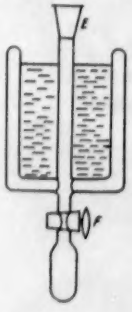


Fig. 2.
Purification of trifluoronitrosomethane.



produced. Irradiation of the gas mixture soon produces a blue colour, which reaches maximum intensity after 20—25 hr.; the surface of the mercury becomes covered with oxide film.

Oxygen is then let into the flask *via C* and *D* until the pressure is atmospheric, and the flask is set aside for 1 hr. to complete the oxidation of unchanged nitric oxide. The gases are slowly (2 hr.) pumped out through three traps cooled by liquid oxygen to separate condensable products from the excess of oxygen, etc., and are then fractionated twice *in vacuo* to remove unchanged trifluoroiodomethane. The trifluoronitrosomethane is freed from carbon dioxide by bubbling it twice through two wash-bottles containing 30% aqueous sodium hydroxide (*ca.* 20 min. per pass). Further fractionation *in vacuo* readily gives a product (Found: *M*, 99. Calc. for $CONF_3$: *M*, 99) contaminated by only traces of trifluoroiodomethane.

Further purification is effected when necessary by use of the apparatus (Fig. 2) constructed from two thick-walled beakers. With the B10 joint *E* attached to a vacuum system, liquid nitrogen is poured into the Dewar vessel to the height indicated and the receiver below tap *F* is cooled in liquid nitrogen. When trifluoronitrosomethane is passed slowly into the evacuated apparatus through *E*, it condenses on the walls and runs down through *F* into the cooled receiver, whereas impurities such as trifluoroiodomethane remain as solid in the centre tube. When drainage of the nitroso-compound has ceased (30 min.), tap *F* is closed, the liquid nitrogen is removed from the Dewar vessel, and the solid impurities, together with some occluded trifluoronitrosomethane, are pumped away through *E* as the temperature rises. The pure trifluoronitrosomethane is then transferred *via F* into the vacuum system and its purity is checked by its infrared spectrum. The ultraviolet spectrum of trifluoronitrosomethane shows only weak absorption in the region 250—300 mμ where trifluoroiodomethane absorbs heavily

(*J.*, 1953, 1764), and contamination with the latter is thus readily detected. The band at 266 mμ in the spectrum of the nitroso-compound reported earlier (*J.*, 1954, 912) is caused partly by trifluoroiodomethane.

In a typical experiment the yield of trifluoronitrosomethane is 85% (7·6 g.) based on the trifluoroiodomethane used (45%).

An Alternative to Mercury in the Preparation of Trifluoronitrosomethane.—Dinitrogen tetroxide reacts rapidly with trifluoronitrosomethane on irradiation (though only slowly in absence of light), and must thus be removed during the reaction of trifluoroiodomethane with nitric oxide. Mercury was used in the original synthesis (*J.*, 1953, 2075) and is still the best for this purpose, but acidified potassium iodide can be used instead, although it gives somewhat lower yields of trifluoronitrosomethane. The 20-l. reaction flask is charged with potassium iodide (200 g.), water (1 l.), and concentrated hydrochloric acid (200 ml.), then freed from air by pumping; trifluoroiodomethane (42·9 g., 0·219 mole) and nitric oxide (13·2 g., 0·438 mole) are then introduced and the flask is irradiated (63 hr.) without shaking. With this technique it was found best to use only the lower 2″ of the ultraviolet light, so that any dinitrogen tetroxide formed was near the surface of the liquid and reacted instantly with it. Fractionation gave unchanged trifluoroiodomethane (24·5 g., 0·125 mole, 57%), carbon dioxide (1·93 g., 0·044 mole), and trifluoronitrosomethane (4·36 g., 0·044 mole, 47%) as volatile products, identified by means of their molecular weights and infrared spectra.

Trifluoronitrosomethane reacts slowly with acidified potassium iodide solution: a sample of the gas (0·0214 g.) in contact with 0·5 ml. of acidified iodide solution (2 g. KI, 2 ml. conc. HCl, 10 ml. H_2O) in a sealed 5-ml. tube in the dark was completely decomposed only after 18 hr., and yielded carbon dioxide (0·17 mmole, 80%) as volatile product. The reaction was accelerated when gas and liquid were intimately mixed by vigorous shaking.

Stability of Trifluoronitrosomethane.—(*a*) Trifluoronitrosomethane stored as vapour in a clean bulb in the dark for 5 weeks failed to show change in properties, molecular weight (98·6. Calc. for $CONF_3$: *M*, 99), or infrared or ultraviolet spectrum. A specimen kept as liquid for several years had undergone <1% decomposition.

(*b*) Trifluoronitrosomethane (0·022 g., 0·223 mmole) and mercury (1 g.), shaken (4 days) in a sealed 5-ml. Pyrex tube covered with tinfoil to exclude light, showed no change in properties (CF_3·NO recovered: 0·022 g. Found: *M*, 98·6). Banus (*loc. cit.*), who reported that the nitroso-compound is completely decomposed in 20 hr. under these conditions, has considerably exaggerated the difficulties of working with perfluoroalkyl nitroso-compounds.

(*c*) The nitroso-compound (0·0215 g., 0·217 mmole) and water (0·5 ml.) were unchanged when shaken (2 days) in a sealed Pyrex tube in absence of light (CF_3·NO recovered: 0·0212 g.).

Trifluoronitrosomethane is completely stable in a vacuum system and can be stored as gas or as liquid with negligible decomposition for many months. Light, alkali, etc., bring about decomposition.

Reaction of Trifluoronitrosomethane with Tetrafluoroethylene.—In a typical low-temperature reaction, trifluoronitrosomethane (1·48 g., 0·015 mole) and tetrafluoroethylene (1·50 g., 0·015 mole) in an evacuated 85-ml. sealed silica tube were kept at −45° (1 hr.), then allowed to warm to room temperature during 24 hr., and finally kept at 20° for 5 days (probably excessive). Fractionation of the volatile products *in vacuo* gave unchanged reactants (8%) and *perfluoro-2-methyl-1 : 2-oxazetidine* (0·85 g., 28%), b. p. (isoteniscope) −6·8° (Found: C, 18·1; N, 7·2%; *M*, 199. C_3ONF_7 requires C, 18·1; N, 7·0%; *M*, 199). The reaction vessel contained an involatile colourless viscous oil (*ca.* 1·8 g., 64%) (see below) on the walls and at the bottom of the tube; the oil sometimes had a gel-like appearance.

In an experiment at room temperature, trifluoronitrosomethane (1·19 g., 0·012 mole) and tetrafluoroethylene (0·60 g., 0·006 mole) kept in a sealed 85-ml. silica tube (14 hr.) gave unchanged tetrafluoroethylene (0·23 g., 37%), unchanged trifluoronitrosomethane (0·82 g., 69%), perfluoro-2-methyl-1 : 2-oxazetidine (0·45 g., 62%), and the oil (0·29 g., 38%). Reaction at a higher temperature thus favours production of the oxazetidine. Other experiments have given similar results.

Properties of Perfluoro-2-methyl-1 : 2-oxazetidine.—This compound is a colourless gas showing only general absorption in the ultra-violet (ε at λ 260, 250, 240, 230, and 220 mμ = 2, 5, 11·5, 24, and 51).

(a) *Stability to aqueous reagents.* Perfluoro-2-methyl-1 : 2-oxazetidine (0·078 g.) and water (0·5 ml.), heated in a sealed 5-ml. Pyrex tube at 155° (14 hr.), gave only unchanged starting material (0·076 g., 97%). When the oxazetidine (0·098 g.) and 10% aqueous sodium hydroxide (1 ml.) were heated in a sealed 5-ml. tube at 110° (14 hr.), 96% (0·094 g.) was recovered

unchanged. Almost quantitative (97%) recovery of the oxazetidine was obtained when it (0·048 g.) and concentrated hydrochloric acid (0·5 ml.) were shaken at room temperature (10 days).

(b) *Irradiation.* Pure perfluoro-2-methyl-1 : 2-oxazetidine showed no signs of decomposition after exposure to ultraviolet radiation (mainly 2537 Å) for 3 days.

(c) *Reaction with hydrogen chloride.* The oxazetidine (0·050 g.) and anhydrous hydrogen chloride (0·018 g.) underwent no reaction at 100° (24 hr.) in a 5-ml. sealed tube.

Perfluoro(methylenemethylamine).—(a) *Preparation from perfluoro-2-methyl-1 : 2-oxazetidine.* The oxazetidine (0·320 g., 1·65 mmoles) was passed at 5 mm. pressure in absence of air through a silica tube (15 mm. internal diam.) heated at 550° over a length of 30 cm., and the reaction products were condensed in a trap cooled by liquid oxygen. Fractionation *in vacuo* gave carbonyl fluoride (0·108 g., 1·63 mmoles) (Found : *M*, 66. Calc. for COF_2 : *M*, 66) and *perfluoro(methylenemethylamine)* (0·217 g., 1·63 mmoles), b. p. (isoteniscope) −33·7° (Found : C, 18·3; N, 10·4%; *M*, 133. C_2NF_5 requires C, 18·1; N, 10·5%; *M*, 133). The carbonyl fluoride was identified by means of its infrared spectrum. Perfluoro(methylenemethylamine) shows only very weak general absorption in the ultraviolet. The oxazetidine has been pyrolysed to perfluoro(methylenemethylamine) on a larger scale in essentially quantitative yield.

(b) *Hydrolysis.* Perfluoro(methylenemethylamine) (0·102 g., 0·77 mmole) and water (0·5 ml., 0·03 mole) were sealed in a 10-ml. Pyrex tube in absence of air and kept at 20° (12 hr.). Fractionation of the volatile products *in vacuo* gave only carbon dioxide (0·067 g., 1·52 mmoles) (Found : *M*, 44. Calc. for CO_2 : *M*, 44). The aqueous solution gave a positive test for fluoride and ammonium ions.

In a second experiment perfluoro(methylenemethylamine) (0·067 g., 0·50 mmole) in a sealed 5-ml. ampoule was inserted in a 3-l. flask which was then evacuated. Water vapour (0·037 g., 2·0 mmoles) was then introduced into the flask; in this volume all the water is in the vapour phase. The tip of the perfluoro(methylenemethylamine) tube was next broken to allow the fluorine compound and the water vapour to mix rapidly. After 24 hr. at 20° the volatile contents of the flask were fractionated *in vacuo* to give unchanged perfluoro(methylenemethylamine) (0·043 g., 0·32 mmole, 64%) identified by its molecular weight and infrared spectrum, silicon tetrafluoride, a small amount of carbon dioxide, and an unknown compound. The N–H band near 3 μ could not be detected in any fraction from the distillation.

The unknown material obtained in the above and several other hydrolysis reactions is volatile (b. p. $< -25°$) and is characterised by infrared absorption at 4·33, 4·38 (doublet), 6·83, and 8·61, 8·65 μ (doublet). The first doublet is readily distinguished from the band of carbon dioxide which appears in this region (4·30 μ), and appears in material which is free from carbon dioxide. The unknown is also produced during the reaction of perfluoro(methylenemethylamine) with silica at 210° (75 hr.), but on the present scale cannot be separated from the silicon tetrafluoride which accompanies it. It is decomposed by aqueous bases.

In a further experiment perfluoro(methylenemethylamine) (0·0350 g.) and 5% aqueous sodium hydroxide (2 ml.), kept at 20° (2 hr.) in a sealed tube, gave fluoride (Found : 70·9, 70·9. Calc. for C_2NF_5 : F, 71·2%), determined as fluorosilicate by thorium nitrate titration. Determination of the fluoride produced by aqueous hydrolysis of perfluoro(methylenemethylamine) gave low results (*e.g.*, Found : F, 67%), since hydrogen fluoride was lost from the aqueous solution during manipulation.

(c) *Reaction with methanol.* Perfluoro(methylenemethylamine) (0·497 g., 3·74 mmoles) and anhydrous methanol (0·960 g., 30 mmoles), sealed in a Pyrex tube *in vacuo*, then warmed to room temperature, reacted exothermally (5 min.). After 40 hr., the volatile products were transferred to a vacuum system and fractionated to give unchanged methanol, dimethyl ether (0·185 g., 4 mmoles; some ether was lost by the method of separation used), and dimethyl carbonate (0·570 g., 6·35 mmoles). The methyl ether, dimethyl carbonate (80% of theory for complete alcoholysis), and ammonium fluorosilicate produced during the reaction were identified by means of their infrared spectra.

Investigation of the Polymer produced from Trifluoronitrosomethane and Tetrafluoroethylene.—The oil referred to above was analysed [Found : C, 18·2; N, 6·9. $(C_3ONF_7)_n$ requires C, 18·1; N, 7·0%]; its ultraviolet spectrum, recorded for a thin film on silica plates, shows only weak general absorption. The oil is substantially insoluble in ether, carbon tetrachloride, chloroform, acetone, benzene, ethanol, light petroleum, trifluoroacetic acid, methyl heptafluorobutyrate, and benzotrifluoride, but readily soluble in perfluoromethyl*cyclo*hexane.

(a) *Behaviour with acid or alkali.* A specimen of the polymer heated with concentrated sulphuric acid failed to undergo reaction. No change could be detected when a sample was heated under reflux with 50% aqueous potassium hydroxide.

(b) *Attempted reduction.* The following methods of reduction were tried: (i) The oil (0·20 g.), intimately mixed with zinc powder then treated with concentrated hydrochloric acid, showed no change even on heating. (ii) The oil (0·20 g.) failed to react with 80% formic acid (2 ml.) in a sealed tube at 110° (24 hr.). (iii) A paste of sodium amalgam and the oil was treated with "AnalaR" methanol under reflux, and, in a separate experiment, with water under reflux. The oil remained unchanged, and products containing fluorine [*e.g.*, (VII), predicted b. p. *ca.* 100°] were not detected. (iv) Zinc-dust distillation of the oil caused only a sudden vigorous decomposition at high temperatures to breakdown products such as carbon dioxide. (v) Lithium aluminium hydride (0·2 g.) in diethyl ether (15 ml.) was without effect on the oil (0·300 g.) during 12 hr. at reflux temperature. The experiment was repeated with perfluoromethyl*cyclo*hexane–ethyl ether as solvent. To the oil (0·80 g.) in perfluoromethyl*cyclo*hexane (15 ml., pretreated with lithium aluminium hydride in ether) was quickly added 0·5M-lithium aluminium hydride in ethyl ether (60 ml.), and the mixture stirred (3 hr.). Hydrolysis, distillation, etc., gave only recovered solvent with no indication of products such as (VII); the oil was recovered unchanged. (vi) An intimate mixture of the oil (0·100 g.) and sulphur (*ca.* 5 g.) was heated at 200° (30 min.) without change. When it was heated with a free flame decomposition occurred, and examination of the volatile products collected in a cooled trap showed them to be carbonyl fluoride and perfluoro(methylenemethylamine) produced by pyrolysis of the oil. No indication of reduction products was obtained.

(c) *Pyrolysis.* In a typical experiment, the polymer (1·56 g.) was placed in a silica tube (25 mm. internal diam.), closed at one end, and with the other end connected, through a trap cooled by liquid oxygen, to an oil-pump. The closed end of the tube was slowly inserted in a horizontal tube furnace (400°) so that the polymer was pyrolysed during a total period of 1 hr. Pyrolysis occurred without charring and without formation of non-condensable gas. The pyrolysate consisted of unchanged polymer (0·15 g.) and volatile products, distillation of which gave carbonyl fluoride (0·472 g., 7·17 mmoles) (Found: *M*, 66. Calc. for COF_2: *M*, 66) and perfluoro(methylenemethylamine) (0·930 g., 7·01 mmoles, 99%) (Found: *M*, 133. Calc. for C_2NF_5: *M*, 133). The products were identified spectroscopically.

(d) *Molecular weight.* An ebullioscopic method with a Cottrell-type apparatus was used with a glycol–water-cooled condenser at −5°. Perfluoromethyl*cyclo*hexane (b. p. 75·8°, d_D^{25} 1·79) was a suitable solvent, and its ebullioscopic constant was determined by use of perfluorohexadecane (Found: C, 23·1; H, 0. Calc. for $C_{16}F_{34}$: C, 23·1; H, 0%) and of perfluoro-1 : 2-di*cyclo*hexylethane (Found: C, 25·2; H, 0. Calc. for $C_{14}F_{26}$: C, 25·3; H, 0%). Spectroscopically pure perfluorohexadecane (1·325 g.), dissolved in perfluoromethyl*cyclo*hexane (50·0 ml.), caused an elevation in b. p. of 0·23°, whence $K = 13·1$. A second determination gave 12·9. Perfluoro-1 : 2-di*cyclo*hexylethane (0·1263 g.), dissolved in perfluoromethyl*cyclo*hexane (5·0 ml.), caused an elevation in b. p. of 0·27°, whence $K = 12·8$; a second determination using 0·1323 g. of the solid gave an elevation of 0·29°, whence $K = 13·1$.

The polymer from trifluoronitrosomethane and tetrafluoroethylene (0·580 g.), dissolved in 50·0 ml. of perfluoromethyl*cyclo*hexane, caused no detectable change in the b. p. of the pure solvent. A b. p. elevation of 0·01° would have been detected, and would correspond to a molecular weight of 7000. The molecular weight of the polymer is thus >7000. A duplicate experiment gave the same result.

For comparison, a short-chain polymer of chlorotrifluoroethylene was used. This had CF_3 or CF_2Cl end-groups, and analysis (Found: C, 19·8, 19·8; H, 0%) indicates $CF_2Cl{\cdot}[CF_2{\cdot}CFCl]_5{\cdot}CF_2{\cdot}CF_2Cl$ (Calc.: C, 19·5%; *M*, 800) or $CF_3{\cdot}[CF_2{\cdot}CFCl]_5{\cdot}CF_2{\cdot}CF_2Cl$ (Calc.: C, 19·9%; *M*, 784). A b. p. elevation of 0·39° was observed when this polymer (2·055 g.) was dissolved in perfluoromethyl*cyclo*hexane (50·0 ml.), whence $M = 765$, in reasonable agreement with the molecular weight of *ca.* 790 deduced from b. p. and analysis. The ebullioscopic method using a fluorocarbon solvent is thus easily sufficiently sensitive to distinguish between compounds (VI) (*M*, 398) and (VIII), and the oil obtained from the reaction of trifluoronitrosomethane and tetrafluoroethylene must thus be a polymer (VIII).

The authors thank Imperial Chemical Industries Limited, General Chemical Division, Widnes, for a generous gift of perfluoromethyl*cyclo*hexane, and Professor M. Stacey, F.R.S., and Dr. J. C. Tatlow for a sample of perfluorodi*cyclo*hexylethane. One of them (D. A. B.) is indebted to Imperial Chemical Industries, Limited, Plastics Division, for a maintenance grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 31st*, 1955.]

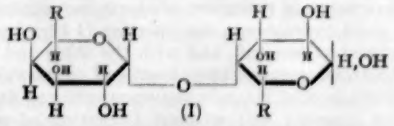
*The Structure of the Oligosaccharides produced by the Enzymic Breakdown of Pectic Acid. Part II.**

By J. K. N. Jones and W. W. Reid.

[Reprint Order No. 6089.]

The disaccharide produced by enzymic hydrolysis of apple pectic acid has been converted into 4-*O*-α-D-galactopyranosyl-D-galactopyranose, and its structure thereby proved.

In Part I * it was shown that the mixture of oligosaccharides produced by the action of the enzymes of *Aspergillus foetidus*, Thom and Raper, on apple pectic acid contained a disaccharide and a trisaccharide. Evidence was advanced which indicated that the disaccharide consisted of two D-galactopyruronic acid residues joined by an α-glycosidic linkage (I; R = CO_2H). This diuronide has now been converted into the corresponding galactobiose (cf. Whistler and Conrad, *J. Amer. Chem. Soc.*, 1954, **76**, 1673).



The major difficulty involved in this transformation was the reduction of the carboxyl groups of the disaccharide without concomitant reduction of the aldehyde group. Protection was required for the aldehyde group during reduction of the carboxyl groups, which could yet be removed later under conditions which did not break the glycosidic linkage. Orthoesters possess such properties : they are apparently not affected by lithium aluminium hydride (cf. Claus and Morgenthau, *J. Amer. Chem. Soc.*, 1951, **73**, 5005) and are hydrolysed with great ease by cold dilute acids (Bott, Haworth, and Hirst, *J.*, 1930, 1395).

Sugar orthoesters are formed under certain conditions from acetobromo-sugars but they are more readily prepared by reaction of the sugar with an orthoester in the presence of an acid catalyst (Astle, Zaslowsky, and Lafyatis, *Ind. Eng. Chem.*, 1954, **46**, 788; Schwarz, *J.*, 1954, 2644; Freudenberg and Jakob, *Ber.*, 1941, **74**, 162). When the disaccharide was shaken with trimethyl orthoformate in the presence of a little hydrochloric acid, it rapidly dissolved and the solution then gave a negative Fehling's test. Removal of the catalyst and esterification of the carboxyl groups was effected by ethereal diazomethane. The resulting syrupy methyl ester derivative was reduced with lithium aluminium hydride, and neutral disaccharide isolated after hydrolysis of the orthoformyl groupings with cold dilute acid. The crystalline disaccharide was identical in all respects with the disaccharide isolated by Whistler and Conrad (*loc. cit.*) from Okra mucilage and is therefore correctly represented by (I; R = CH_2·OH), and the digalacturonic acid by (I; R = CO_2H).

Experimental

The following solvent systems were used in chromatographic separations : (*a*) ethyl acetate–acetic acid–water (9 : 2 : 2, v/v), (*b*) *n*-butanol–pyridine–water (10 : 3 : 3, v/v), and (*c*) *n*-butanol–ethanol–water (4 : 1 : 2, v/v). *p*-Anisidine hydrochloride (1%, w/v) in *n*-butanol or silver nitrate solution in acetone followed by sodium hydroxide in ethanol was used to locate the sugars. Optical rotations were determined at 20° ± 2°. Solvents were evaporated under reduced pressure.

Preparation of the Orthoester.—The crystalline diuronide (1·95 g.) was added to trimethyl orthoformate (40 c.c.) to which concentrated hydrochloric acid (7 drops) had been added. The solid slowly dissolved when the mixture was shaken, and dissolution was complete in 15 hr. The cooled solution was neutralized by the addition of diazomethane in ether, and the resultant lemon-yellow solution then evaporated to a syrup which was dissolved in dioxan (10 c.c.). This

* Part I, *J.*, 1954, 1361.

solution was added with stirring to a solution of lithium aluminium hydride (2 g.) in dioxan. After 2 hr. excess of the hydride was destroyed by the addition, first, of ethyl acetate and then of water. The slurry was filtered and the filtrate evaporated to a syrup which was extracted with acetone. The acetone extracts were evaporated to a syrup, and the residue extracted with chloroform. Removal of the solvent left an oil (1·6 g.). Chromatographic examination (solvents *b* and *c*) indicated that it was a complex mixture. The syrup dissolved in water to yield a milky neutral solution containing derivatives of the required galactobiose.

Hydrolysis of the Galactobiose Derivatives.—The syrup was dissolved in 0·1N-hydrochloric acid (20 c.c.) and the solution kept at room temperature for 24 hr. It was not possible to follow any change in optical rotation but chromatographic examination indicated that hydrolysis was taking place with formation of traces of galactose and a sugar which had the chromatographic characteristics of a disaccharide. After 24 hr. the solution was passed down a column of Amberlite resin IR-4B (acetate form), and the effluent from the column concentrated to a syrup. Addition of acetone–methanol caused the syrup to dissolve and in a day or so crystals of 4-*O*-α-D-galactopyranosyl-D-galactose separated. The total yield of product after recrystallisation from methanol–*n*-butanol–water mixture was 0·31 g. This substance moved at the same rate as an authentic specimen which was kindly provided by Dr. R. L. Whistler of Purdue University. Its rate of movement relative to lactose was 1·0 in solvent (*b*) and 1·1 in solvent (*a*). [The corresponding 1 : 3-β-linked isomer kindly provided by Dr. A. S. Perlin moved at the same rate as lactose in solvent (*a*).] It had m. p. 210°, with sintering at 200°, not altered on admixture with an authentic specimen, and $[\alpha]_D$ + 186 ⟶ + 173° (*c*, 1·2) (6 hr., equilib.). The *X*-ray picture was identical with that of an authentic specimen (Found : C, 42·2; H, 6·4. Calc. for $C_{12}H_{22}O_{11}$: C, 42·1; H, 6·4%). Attempts to make an osazone yielded oils.

The authors thank Dr. R. L. Whistler for the gift of 4-*O*-α-D-galactopyranosyl-D-galactose, Dr. A. S. Perlin of the National Research Council, Saskatoon, for the gift of the β-1 : 3-isomer, and the National Research Council, Canada, for a grant.

QUEEN'S UNIVERSITY, KINGSTON, ONTARIO, CANADA.
RESEARCH DEPARTMENT, H. W. CARTER & COMPANY LIMITED, COLEFORD, GLOUCESTERSHIRE.
(Present Address : W. W. R., RESEARCH DEPARTMENT, CARRERAS LIMITED, STANHOPE STREET, LONDON, N.W.1.)
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Steroids and Walden Inversion. Part XXV. A Kinetic Study of the Methanolysis of Cholesteryl Toluene-*p*-sulphonate in the Presence of Methoxide Ions.*

By C. W. SHOPPEE and D. T. WESTCOTT.

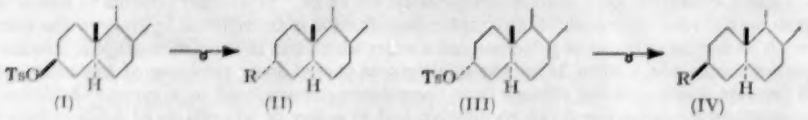
[Reprint Order No. 6127.]

Methanolysis of cholesteryl toluene-*p*-sulphonate in the presence of methoxide ions gives cholesteryl methyl ether, 6β-methoxy-3 : 5-*cyclo*-cholestane, and cholesta-3 : 5-diene, unaccompanied by *epi*cholesteryl methyl ether. A kinetic study shows that the reaction is of the first order with respect to the toluene-*p*-sulphonate with $k_1 = 0{\cdot}0043$ min.$^{-1}$; since the rate of methanolysis under identical conditions but in the absence of methoxide ions has been found to be $k_1 = 0{\cdot}0046$ min.$^{-1}$ (Pearson, King, and Langer, *J. Amer. Chem. Soc.*, 1951, **73**, 4149), these solvolyses occur by a unimolecular mechanism (S_N1). The methoxide ion, in contrast to ions of type NR_2^-, is too weakly nucleophilic to compete by an S_N2 substitution process with the π-electron-facilitated S_N1 substitution.

NUCLEOPHILIC substitution at $C_{(3)}$ in saturated steroids usually proceeds with inversion of configuration at $C_{(3)}$ and therefore by a bimolecular mechanism (S_N2). Thus, cholestan-3β-yl toluene-*p*-sulphonate (I; *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$ equatorial) by methanolysis at 65° gives

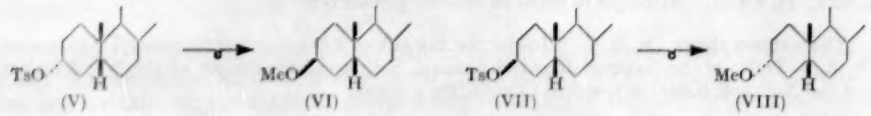
* Part XXIV, *J.*, 1955, 1375.

3α-methoxycholestane (II; R = MeO) (73%), together with a mixture of cholest-2- and -3-ene (17%), but unaccompanied by the 3β-epimeride (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147; Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937), whilst use of pyridine or piperidine at 100° affords *N*-cholestan-3α-ylpyridinium toluene-*p*-sulphonate (II; R = $C_5H_5N^+$}*p*-$C_6H_4Me{\cdot}SO_2{\cdot}O^-$) or *N*-cholestan-3α-ylpiperidine (II; R = $C_5H_{10}N{\cdot}$) (King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 3338). Conversely cholestan-3α-yl toluene-*p*-sulphonate (III; *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$ axial) by methanolysis at 65° gives 3β-methoxycholestane (IV;



(I) (II) (III) (IV)

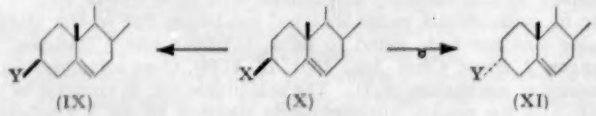
R = MeO) (23%), together with a mixture of cholest-2- and -3-ene (69%), but unaccompanied by the 3α-epimeride (Nace, *loc. cit.*), whilst use of pyridine or piperidine at 100° furnishes *N*-cholestan-3β-ylpyridinium toluene-*p*-sulphonate (IV; R = $C_5H_5N^+$}*p*-$C_6H_4Me{\cdot}SO_2{\cdot}O^-$) or *N*-cholestan-3β-ylpiperidine (IV; R = $C_5H_{10}N$) (King and Bigelow, *loc. cit.*). Similarly, coprostan-3α-yl toluene-*p*-sulphonate (V; *p*-$C_6H_4Me{\cdot}SO_2O$ equatorial) by methanolysis furnishes 3β-methoxycoprostane (VI) (82%), and coprost-2-ene (18%), unaccompanied by the 3α-epimeride (D. D. Evans and Shoppee, *J.*, 1953, 540),



(V) (VI) (VII) (VIII)

whilst coprostan-3β-yl toluene-*p*-sulphonate (VII; *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$ axial) yields a little 3α-methoxycoprostane (VIII) (J. R. Lewis and Shoppee, *J.*, 1955, 1375) and much coprost-2-ene (~90%). The pattern of reaction is thus inversion accompanied by elimination with effectively complete absence of racemisation.

Until recently it was thought that nucleophilic replacement at $C_{(3)}$ in 3β-substituted Δ^5-steroids proceeds with complete retention of configuration by a unimolecular mechanism (S_N1) involving participation of the π-electrons of the 5 : 6-double bond (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 475; Davies, Meecham, and Shoppee, *J.*, 1955, 679). Thus, cholesteryl chloride and toluene-*p*-sulphonate (X; X = Cl or *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$ equatorial) by methanolysis give cholesteryl methyl ether (IX; Y = MeO) (~90%) unaccompanied by *epi*cholesteryl methyl ether (Diels and Blumberg, *Ber.*, 1911, **44**, 2874; Stoll, *loc. cit.*); the reaction at 34·8° has been shown to be of the first order with respect to the toluene-*p*-sulphonate with $k_1 = 0{\cdot}0046$ min.$^{-1}$ (Pearson, King, and Langer, *J. Amer. Chem. Soc.*, 1951, **73**, 4149) and so presumably proceeds by a unimolecular mechanism. Similar observations have been made for hydrolysis (Beynon, Heilbron, and Spring, *J.*, 1936, 907) and acetolysis (Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137; Bergmann, *ibid.*, 1938, **60**,



(IX) (X) (XI)

1996; Shoppee, *J.*, 1946, 1147; Shoppee and Summers, *J.*, 1952, 3361). Likewise, cholesteryl bromide, iodide, and toluene-*p*-sulphonate (X; X = Br, I, or *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) react with pyridine at 120° to give the quaternary salt (IX; Y = $C_5H_5N^+$}*p*-$C_6H_4{\cdot}SO_2{\cdot}O^-$) (71%) with cholesta-3 : 5-diene (21%) (King and Regan, *J. Amer. Chem. Soc.*, 1952, **74**, 5617).

The pattern of reaction for substitution of 3β-substituted Δ^5-steroids thus appears to

be retention of configuration, absence of racemisation, and little or no elimination. It has, however, been shown that, for substitution of 3β-substituted Δ^5-steroids by sufficiently powerful nucleophiles [Y = $^-CH(CO_2R)_2$, NH_2^-, NHR^-, NR_2^-] under appropriate conditions, the unimolecular reaction (X ⟶ IX) can be accompanied, or even largely superseded, by the bimolecular reaction with inversion of configuration (X ⟶ XI), in which the π-electrons of the double bond do not participate (Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694).

In 3α-substituted Δ^5-steroids on account of the molecular geometry the π-electrons of the 5 : 6-double bond are unable effectively to participate in reactions at $C_{(3)}$, and unimolecular heterolysis generally leads to elimination (*E*1) with formation of 3 : 5-dienes rather than to substitution (S_N1). Thus the methanolysis (or ethanolysis) of *epi*cholesteryl toluene-*p*-sulphonate (XIII; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$ axial) gives cholesta-3 : 5-diene (XII) (76%), and, by rearrangement involving hydrogen migration, 4β-methoxycholest-5-ene

(XII) (XIII) (XIV)

and 6β-methoxycholest-4-ene (7%) (Evans and Shoppee, *loc. cit.*), and takes place by a unimolecular mechanism (King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 6238). Similarly, the acetolysis of *epi*cholesteryl chloride, bromide, and toluene-*p*-sulphonate (XIII; X = Cl, Br, or *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) furnishes cholesta-3 : 5-diene (XII) (92—99%) Evans and Shoppee, *loc. cit.*) by a unimolecular mechanism (Shoppee and D. F. Williams, *J.*, 1955, 686). In none of these reactions has any detectable amount of a 3α- or a 3β-substitution product been reported. If, however, *epi*cholesteryl toluene-*p*-sulphonate is treated with pyridine or piperidine at 100°, then although much elimination occurs to give cholesta-3 : 5-diene (XII) (~75%), there is also bimolecular substitution at $C_{(3)}$ with inversion of configuration to give 3β-substituted Δ^5-derivatives [XIV; Z = $C_5H_5N^+$}*p*-$C_6H_4Me{\cdot}SO_2O^-$ (8%) or $C_5H_{10}N$ (11%)] (King and Bigelow, *loc. cit.*). The reversion of the reaction pattern to that characteristic of the saturated series (inversion + elimination) is consistent with the inability of the π-electrons in 3α-substituted Δ_5-steroids to intervene effectively in reactions at $C_{(3)}$, as suggested by Shoppee and Williams (*loc. cit.*).

King and Bigelow observed that the ethanolysis of *epi*cholesteryl toluene-*p*-sulphonate in the presence of ethoxide ions at 34·8° exhibited second-order kinetics (*loc. cit.*; Fig. 3); they concluded that the ethoxide ion can react directly with the toluene-*p*-sulphonate, although they did not attempt to isolate the product of such a reaction (XIV; Z = EtO). It seemed of interest to investigate the parallel but converse case of the solvolysis of cholesteryl toluene-*p*-sulphonate in methanol (dielectric constant 32) in the presence of methoxide ions at 35°. The product, on repeated chromatography, gave cholesteryl methyl ether (IX; Y = MeO) formed by unimolecular substitution with retention of configuration, 6β-methoxy-3 : 5-*cyclo*cholestane formed by rearrangement, and cholesta-3 : 5-diene (XII) formed by elimination. In methanol containing 75% of dioxan (dielectric constant 4·1) at 35°, and in methanol containing 75% of toluene (dielectric constant ~3) at 35° the same three products only were obtained; when similar experiments were carried out under reflux, *i.e.*, at ~100° and ~110°, mixtures of cholesteryl methyl ether and 6β-methoxy-3 : 5-*cyclo*cholestane but no cholesta-3 : 5-diene were obtained. In none of these experiments could *epi*cholesteryl methyl ether (XI; Y = MeO), which should result from bimolecular substitution, be isolated.

The kinetic measurements were carried out at 35° in methanolic sodium methoxide, containing chloroform to give a homogeneous solution [MeOH/$CHCl_3$(10 : 1)], using a conductance method (Pearson, *J. Amer. Chem. Soc.*, 1947, **69**, 3100). For the reaction: $RX + Y^- \xrightarrow{k_1} RY + X^-$, the concentrations and conductances at zero time, time *t*, and infinite time are as tabulated. It follows that $a = (1/R_0 - 1/R_\infty)Z$, and $x = (1/R_0 - 1/R)Z$, where *Z* is a proportionality constant $A/[\lambda_{Y^-} - \lambda_{X^-}]$, and R_0, *R*, and R_∞ are the

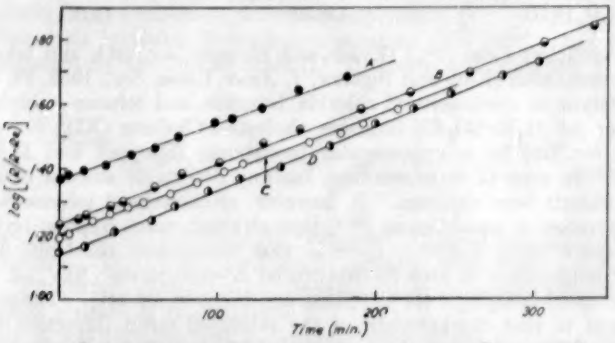
resistances at zero time, time t, and infinite time, whilst the usual first-order rate equation has the form

$$k_1 = \frac{2{\cdot}303}{t} \log \frac{R(R_0 - R_\infty)}{R_0(R - R_\infty)}$$

Since $(R_0 - R_\infty)/R_0$ is constant, the plot of log $[R/R - R_\infty)]$ against time gives the first-order rate constant; the results are shown in the Figure.

The reaction is clearly of the first order with respect to cholesteryl toluene-*p*-sulphonate with an average rate $k_1 = 0{\cdot}0043$ min.$^{-1}$. This value is close to that, $k_1 = 0{\cdot}0046$ min.$^{-1}$, found under identical conditions for the methanolysis of cholesteryl toluene-*p*-sulphonate in the absence of methoxide ions (Pearson, King, and Langer, *loc. cit.*); it is consistent with a unimolecular mechanism involving a rate-determining heterolysis and indicates that the methoxide ion does not react directly with cholesteryl toluene-*p*-sulphonate. This behaviour is in sharp contrast with the direct reaction of the methoxide ion with *epi*-cholesteryl toluene-*p*-sulphonate, and suggests that the methoxide ion is too weakly

Methanolysis of cholesteryl toluene-p-*sulphonate at* 35° ± 0·1°.



Curve	*A*	*B*	*C*	*D*
Toluenesulphonate concn. (10^{-3}M)	1·11	1·48	1·50	1·24
NaOMe concn. (10^{-3}M)	6·60	5·73	5·20	3·21
$10^3 k_1$ (min.$^{-1}$)	4·03	4·34	4·05	4·56

Time	Concentrations [RX]	[Y$^-$]	[RY]	[X$^-$]	Conductances
0	a	b	0	0	$1/R_0 = A[\lambda_{Y^-} . b]$
t	$a - x$	$b - x$	x	x	$1/R = A[\lambda_{Y^-}(b - x) + \lambda_{X^-} . x]$
∞	0	$b - a$	a	a	$1/R\infty = A[\lambda_{Y^-}(b - a) + \lambda_{X^-} . a]$

nucleophilic to compete with the π-electron-facilitated unimolecular heterolysis of a 3β-substituted Δ^5-steroid (Shoppee and Summers, *J.*, 1952, 3367). This conclusion is in agreement with the known low nucleophilic power of the methoxide ion as disclosed by the sequence of nucleophilic power: $SPh^- \gg$ piperidine $> OMe^- > OPh^- \gg OH^-$ found by Bunnett and Davis (*J. Amer. Chem. Soc.*, 1954, **76**, 3011).

Experimental

For general experimental directions see *J.*, 1955, 1375. $[\alpha]_D$ are in $CHCl_3$, with $c \sim 1{\cdot}0$.

Anhydrous Methanol.—Methanol was distilled over potassium hydroxide pellets, and then refluxed over lime for 24 hr.; finally, it was dried by treatment with magnesium (Lund and Bjerrum, *Ber.*, 1931, **64**, 210). For preparation of sodium methoxide solutions, dry nitrogen was bubbled for 0·5 hr. through methanol, which thereafter was allowed to drip on to sodium, at a speed sufficient to maintain refluxing, in an atmosphere of nitrogen.

Reaction of Cholesteryl Toluene-p-*sulphonate with Sodium Methoxide in Methanol.*—Cholesteryl toluene-*p*-sulphonate (1·238 g.) was dissolved in chloroform (5 c.c.), methanolic 0·039N-sodium methoxide (100 c.c.) was added under nitrogen, and further chloroform (5 c.c.) was

added to give a homogeneous solution 0·021M with respect to toluenesulphonate; the ampoule was sealed and left at 35° for 20 hr. The product was isolated in the usual way, and chromatographed on aluminium oxide (45 g.) in pentane. Elution with pentane (4 × 100 c.c.) gave fractions: A1, trace of oil; A2 (95 mg.), crude cholesta-3 : 5-diene giving a positive Rosenheim test; A3 (32 mg.), m. p. 72°, after recrystallisation from acetone; A4 (78 mg.), m. p. 82°, $[\alpha]_D$ −41°, after recrystallisation from acetone. Elution with benzene–pentane (1 : 19; 5 × 100 c.c.) gave fractions: B1, B2, B3, B4 (159 mg.; 244 mg.; 122 mg.; 69 mg.), consisting of 3β-methoxycholest-5-ene, which had m. p. 83—84°, $[\alpha]_D$ −45°, after recrystallisation from acetone; B5 contained only traces of material. Elution with benzene–pentane (1 : 9; 2 × 100 c.c.) gave fractions: C1, C2 (34 mg., 25 mg.), consisting of 3β-methoxycholest-5-ene, m p. 82—84°, $[\alpha]_D$ −46°; further elution with benzene gave insignificant amounts of material.

The recrystallised fractions A2, A3, and A4 were combined (188 mg.) and rechromatographed on aluminium oxide (20 g.) in pentane. Elution with pentane (5 × 20 c.c.) gave fractions: D1 (9 mg., positive Rosenheim test); D2 and D3 (33 mg., 30 mg.), cholesta-3 : 5-diene, m. p. 80°, $[\alpha]_D$ −114°, giving positive Rosenheim tests, after recrystallisation from acetone: D4 and D5 (13 mg., 17 mg.), 6β-methoxy-3 : 5-*cyclo*cholestane, m. p. 79°, $[\alpha]_D$ +54°, after recrystallisation from acetone; D6, traces. Elution with benzene–pentane (1 : 1) gave 3β-methoxycholest 5-ene, m. p. 82°, $[\alpha]_D$ −46° (82 mg.), after recrystallisation from acetone. A second experiment furnished only the same three products.

Kinetic measurements. The rate of methanolysis was measured conductometrically at 35·0° ± 0·1° with a conventional bridge assembly which incorporated a 1000-cycle oscillator. Resistance measurements were made to ±1 ohm. The cell employed was after the design of Jones and Bollinger (*J. Amer. Chem. Soc.*, 1931, **53**, 441). The electrodes were lightly platinised and the cell constant was approx. 5 cm.$^{-1}$.

In different runs the concentration of cholesteryl toluene-*p*-sulphontae was maintained approx. 1·5 × 10^{-3}M, whilst that of the sodium methoxide was varied in the range 3—7 × 10^{-3}M; the latter solutions were standardised immediately before use against 0·01N-hydrochloric acid. The methanolic sodium methoxide was introduced into the cell and allowed to attain 35°, and a weighed amount of the ester, dissolved in the volume of purified chloroform required to give the ratio MeOH : $CHCl_3$ = 10 : 1, was added. Resistances were determined at appropriate intervals. The results are given in the Figure and its legend.

*Reaction of Cholesteryl Toluene-*p*-sulphonate with Sodium Methoxide in Dioxan and Toluene.*—(*a*) The ester (1·95 g.), dissolved in dioxan (75 c.c.), was treated with methanolic 0·041N-sodium methoxide (25 c.c.) at 35° for 37 hr.; the concentration of the ester was 0·036N. The product was isolated in the usual way, and chromatographed on aluminium oxide in pentane. Elution with pentane gave fractions A1—5 (12, 393, 209, 79, and 44 mg.) all giving the Rosenheim test; use of benzene–pentane (1 : 19) gave fractions B1 and B2 (83, 10 mg.) as oils; use of benzene–pentane (1 : 9) gave no material, but use of benzene–pentane (1 : 3) yielded fractions C1 (37 mg.) and C2 (30 mg.) consisting of slightly impure 3β-methoxycholest-5-ene which had m. p. 70—72°, $[\alpha]_D$ −39°, and m. p. 74—76°, $[\alpha]_D$ −40°, after recrystallisation from acetone. Elution with benzene gave no material, but use of acetone gave some cholesteryl toluene-*p*-sulphonate, m. p. and mixed m. p. 132°. Fractions A2—5 were united and rechromatographed: exhaustive elution with pentane gave fractions E1, E2, consisting of cholesta-3 : 5-diene (257, 166 mg.), m. p. 80°, $[\alpha]_D$ −114°, after recrystallisation from acetone, E3, E4, and E5 consisting essentially of 6β-methoxy-3 : 5-*cyclo*cholestane (99, 31, 17 mg.), m. p. 72°, $[\alpha]_D$ +30°, m. p. 69°, $[\alpha]_D$ +37°, and m. p. 74° respectively, after recrystallisation from acetone. Fractions B1 and B2, and the mother-liquors from the crystallisation of fractions C1 and C2 were combined and rechromatographed; elution with pentane gave fractions F1 and F2 consisting of 6β-methoxy-3 : 5-*cyclo*cholestane (24 mg., —), m. p. 74°, $[\alpha]_D$ +50°, and m. p. 76°, $[\alpha]_D$ +51° respectively, after recrystallisation from acetone. Further elution with pentane and benzene–pentane (1 : 19, 1 : 9) yielded no material, but use of benzene–pentane (1 : 4) gave fractions G1, G2, and G3 (8, 10, and 6 mg.) which were united and recrystallised from acetone to give 3β-methoxycholest-5-ene, m. p. and mixed m. p. 81—84°, $[\alpha]_D$ −46°.

(*b*) The ester (2·43 g.), dissolved in dioxan (75 c.c.), was heated at 100° with methanolic 0·06N-sodium methoxide (25 c.c.) under nitrogen for 6 hr. Chromatography of the product on aluminium oxide gave by elution with pentane (3 × 200 c.c.) fractions: A1 (346 mg.), 6β-methoxy-3 : 5-*cyclo*cholestane, m. p. 76—78°, $[\alpha]_D$ +53° after crystallisation from acetone; A2 (1·17 g.), m. p. 66°, $[\alpha]_D$ +32°, after crystallisation from acetone; A3 (40 mg.). Use of benzene gave fraction B1 (40 mg.), an oil. Fraction A2 was rechromatographed; elution with pentane (3 × 100 c.c.; 2 × 50 c.c.) gave fractions: C1 (493 mg.), m. p. 76°; C2 (417 mg.), m. p. 76—79°;

C3 (170 mg.), m. p. 79—80°; C4 and C5, m. p. 81°; these fractions were crystallised from acetone and gave no m. p. depressions on admixture with 3β-methoxycholest-5-ene although giving depressions of ~15° on admixture with 3α-methoxycholest-5-ene. Fractions A3 and B1 were united and rechromatographed; elution with pentane gave no material, but use of benzene–pentane (1 : 19) gave fractions D1, D2, and D3, which after examination were combined and recrystallised from acetone to yield 3β-methoxycholest-5-ene, m. p. and mixed m. p. 80°, $[\alpha]_D$ −45°; fraction D4 (25 mg.) also consisted of this substance, m. p. 78—80°, mixed m. p. 80°. No cholesta-3 : 5-diene was detected, nor could 3α-methoxycholest-5-ene be isolated.

(*c*) The ester (1·024 g.), dissolved in toluene (75 c.c.), was treated with methanolic 0·022N-sodium methoxide (25 c.c.) under nitrogen at 35° for 37 hr. The product was isolated in the usual way, and chromatographed on aluminium oxide in pentane. Elution with pentane (4 × 100 c.c.) gave fractions A1 and A2 (262 mg., 239 mg.) consisting mainly of cholesta-3 : 5-diene, m. p. 66° after recrystallisation from acetone, giving an immediate positive Rosenheim reaction, then A3 (38 mg.), and A4 (28 mg.), whilst use of benzene–pentane (1 : 19) gave fraction B1 (58 mg.), consisting of nearly pure 3β-methoxycholest-5-ene, m. p. and mixed m. p. 81°, $[\alpha]_D$ −44°; no further material was eluted except by acetone which furnished a small quantity of cholesteryl toluene-*p*-sulphonate, m. p. 131°. The considerable mother-liquors from fractions A1 and A2 were united and rechromatographed, to give by elution with pentane fractions as follows: C1 and C2 (184 mg.; 115 mg.), m. p. 66—70° and 69—71°, $[\alpha]_D$ +34°, after recrystallisation from acetone, giving the Rosenheim test after a long induction period and consisting of 6β-methoxy-3 : 5-*cyclo*cholestane contaminated by cholesta-3 : 5-diene; C3 (69 mg.) and C4 (43 mg.) consisting of nearly pure 6β-methoxy-3 : 5-*cyclo*cholestane, m. p. 74—76°, mixed m. p. 76—79°, after recrystallisation from acetone. Elution with benzene–pentane (1 : 9) gave only 23 mg. of material, m. p. 72°. Fractions C1 and C2 were united and rechromatographed, to give by elution with pentane fractions: E1 (10 mg.), oil; E2 (34 mg.), giving a positive Rosenheim test; E3 (66 mg.); E4 and E5 (47 mg.; 27 mg.) consisting of 6β-methoxy-3 : 5-*cyclo*cholestane, m. p. 74°, m. p. 76—79°; all material was then removed from the column by elution with acetone, and the material obtained (70 mg.) chromatographed anew. Elution with pentane gave fractions: F1 and F2 (8 mg.; 23 mg.), m. p. 80°, m. p. 82°, which after examination were combined and recrystallised from acetone to give 3β-methoxycholest-5-ene, m. p. and mixed m. p. 82°; F3 (16 mg.), m p. 70—74°, and F4 (8 mg.), m. p. 64°, too small for further purification.

(*d*) The ester (0·88 g.), dissolved in toluene (75 c.c.), was heated under reflux in an atmosphere of dry nitrogen with methanolic 0·022N-sodium methoxide (25 c.c.) for 5 hr. Isolation of the product in the usual way and chromatography on aluminium oxide gave by elution with pentane (5 × 100 c.c.) fractions: A1 (192 mg.), m. p. 79°, $[\alpha]_D$ +54°; A2 (185 mg.), m. p. 79°; A3 (64 mg.), m. p. 77°; A4 (78 mg.), m. p. 77°, $[\alpha]_D$ +53°; all these fractions were crystallised from acetone and consisted of 6β-methoxy-3 : 5-*cyclo*cholestane. Elution with benzene–pentane (1 : 4; 3 × 100 c.c.) gave fractions: B1 (58 mg.), a mixture, m. p. 74°, not further examined; B2 (48 mg.), m. p. 82—84°; B3 (20 mg.), m. p. 81°; the last two fractions were recrystallised from acetone and consisted of 3β-methoxycholest-5-ene. Neither cholesta-3 : 5-diene nor 3α-methoxycholest-5-ene could be isolated.

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UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA. [*Received, February 14th*, 1955.]

The Migration of Aromatic Nitro-groups.

By K. H. Pausacker and J. G. Scroggie.

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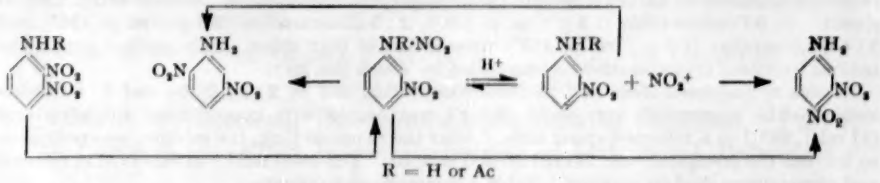
2 : 3-Dinitroacetanilide, 2 : 3-dinitroaniline, and 2 : 3-dinitrophenol undergo rearrangement when heated with concentrated sulphuric acid, but the corresponding 2 : 5- and 3 : 4-disubstituted compounds do not. A mechanism is suggested for the reaction.

Welsh (*J. Amer. Chem. Soc.*, 1941, **63**, 3276) reported that 2 : 3-dinitroacetanilide is hydrolysed to 2 : 3-dinitroaniline in 60% yield when heated with concentrated sulphuric acid at 110° for 5 min. Surprisingly, it has now been found that, when the mixture is heated for 20 min., 2 : 5-dinitroaniline (12%) is also formed in addition to the expected 2 : 3-dinitroaniline (57%). Furthermore, after 8 hours' heating of the mixture 2 : 3-dinitroaniline is not isolated and only 2 : 5-dinitroaniline (47%) and 3 : 4-dinitroaniline (24%) are obtained. An intermediate time of heating yields a mixture of the three dinitroanilines. Under the same conditions, 2 : 3-dinitroaniline is similarly rearranged. Thus, when 2 : 3-dinitroaniline is heated with sulphuric acid for 8 hr., almost the same yields as before of 2 : 5-dinitroaniline (42%) and 3 : 4-dinitroaniline (23%) are isolated. However, this rearrangement is apparently slower than that observed with 2 : 3-dinitroacetanilide, as lower conversions are obtained with shorter times of heating (see Experimental section). Both 2 : 5- and 3 : 4-dinitroaniline can be recovered quantitatively after heating with sulphuric acid.

When 2 : 3-dinitroaniline is heated with sulphuric acid in the presence of an excess of anisole for 4 hr., 2 : 5-dinitroaniline (26%), *N*-methyl-2 : 5-dinitroaniline (5%), 3 : 4-dinitroaniline (12%), 2 : 3-dinitroaniline (16%), and *m*-nitroaniline (13%) are formed. The formation of *N*-methyl-2 : 5-dinitroaniline is of interest, as it involves a transmethylation which is effected by demethylation of the anisole and subsequent methylation of 2 : 5-dinitroaniline. Nitrophenols or nitroanisoles were not isolated, presumably owing to sulphonation and oxidation under the conditions used.

The following mechanism is proposed for the rearrangement :



All reactants are considered to be protonated in the sulphuric acid medium (cf. Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 40). The first stage is the conversion of the 2 : 3-dinitro-compounds into the corresponding 3 : *N*-dinitro-compounds *. This reaction, which is a reversal of the normal conversion of *N*-nitro-compounds into *C*-nitro-compounds, is assumed to be brought about by steric crowding of the 2-nitro-group, and is expected to proceed *via* a reversal of the mechanism proposed by Hughes (see Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 628) for the nitramine rearrangement. The formation of the *N*-nitro-compound is assumed to take place more readily with 2 : 3-dinitroacetanilide than with 2 : 3-dinitroaniline. The steric factor is of obvious importance, as neither 2 : 5- nor 3 : 4-dinitroaniline rearranges under the conditions used. In addition, a highly acidic medium is necessary, since alcoholic hydrochloric acid converts 2 : 3-dinitroacetanilide into 2 : 3-dinitroaniline quantitatively.

The *N*-nitro-compound formed may, in part, rearrange intramolecularly to 2 : 5-dinitroaniline (cf. Hughes and Jones, *J.*, 1950, 2678; Hughes, *op. cit.*), and it is also possible that some 3 : 4-dinitroaniline may be formed thus. However, this cannot be

* The authors are grateful to a Referee for this suggestion.

settled until more is known about the mechanism of the rearrangement of *N*-nitro-compounds to the corresponding *p*-nitro-compounds.

In addition, part of the *N*-nitro-compound must undergo acidolysis to *m*-nitroaniline (or *m*-nitroacetanilide) and a nitrating agent (assumed to be the nitronium ion). This is shown by the fact that *m*-nitroaniline is isolated from the reaction mixture when anisole is added. Hughes and Jones (*loc. cit.*) have established that *N*-methyl-2 : 4 : *N*-trinitroaniline undergoes acidolysis in either pure or aqueous (80%) sulphuric acid.

The nitrating agent produced is then assumed to react with the *m*-nitroaniline (or *m*-nitroacetanilide), finally forming 2 : 5- and 3 : 4-dinitroaniline. The formation of 2 : 5-dinitroaniline in this way is not regarded as appreciable, since the yield of 2 : 5-dinitroaniline (partly as the *N*-methyl derivative) is almost unchanged in the presence of anisole. However, this reaction appears important in the formation of 3 : 4-dinitroaniline, as a greatly reduced yield of this compound is obtained in the presence of anisole.

It has also been found that 2 : 3-dinitrophenol is partly converted into 2 : 5-dinitrophenol when heated with concentrated sulphuric acid, whereas 2 : 5- and 3 : 4-dinitrophenol are not rearranged. Again, only the sterically-hindered nitro-group is capable of migration.

Since the completion of this work, Dr. W. L. Mosby has kindly drawn our attention to a paper by Frisch, Silverman, and Bogert (*J. Amer. Chem. Soc.*, 1943, **65**, 2432), who have shown that 4-amino-3-nitroveratrole is partly rearranged to 4-amino-5-nitroveratrole when heated with acetic acid–phosphoric acid. Although no investigation of the mechanism was made, this rearrangement further supports the concept that the lability of the *o*-nitro-group is dependent on both a high acidity and steric hindrance.

Experimental

M. p.s are corrected. Analyses are by Dr. W. Zimmermann.

Nitration of m-*Nitroacetanilide.*—*m*-Nitroacetanilide (85 g.), dissolved in small portions in fuming nitric acid (300 ml.; *d* 1·50), was slowly added to stirred concentrated sulphuric acid (300 ml.), the temperature being maintained at 0—5° by the addition of solid CO_2. The mixture was then poured on ice (1 kg.) and the product filtered off, washed, and dried. Crystallisation of the crude product from ethanol (1·5 l.) gave 2 : 3-dinitroacetanilide (34 g.; m. p. 188°). The filtrate was refluxed (4 hr.) with concentrated hydrochloric acid (200 ml.) and, after evaporation, the residue was dissolved in benzene and chromatographed on alumina, benzene being used as eluant. 2 : 5-Dinitroaniline (7·8 g.; m. p. 136°), 2 : 3-dinitroaniline (7·6 g.; m. p. 126°), and 3 : 4-dinitroaniline (4·3 g.; m. p. 153°) were eluted in that order. This method avoids the tedious fractional crystallisation recommended by Welsh (*loc. cit.*).

Action of Sulphuric Acid on 2 : 3-*Dinitroacetanilide, and on* 2 : 3-, 2 : 5-, *and* 3 : 4-*Dinitroaniline.*—The appropriate compound (5·0 g.) was heated with concentrated sulphuric acid (11 ml.; 98%) in a toluene-vapour bath. After the requisite time, the mixture was poured on to ice and the precipitate was filtered off and washed. The dried solid was dissolved in benzene and chromatographed on alumina. Table 1 summarises the results.

Table 1.

Compound	Time (hr.)	Yield of dinitroaniline (%) 2 : 3-	2 : 5-	3 : 4-	Compound	Time (hr.)	Yield of dinitroaniline (%) 2 : 3-	2 : 5-	3 : 4-
2 : 3-Dinitroacetanilide	0·33	57	12	0	2 : 3-Dinitroaniline	0·33	96	4	0
	4·25	5	46	23		4·25	20	34	18
	8·00	0	47	24		8·00	0	42	23
					2 : 5-Dinitroaniline	7·5	0	100	0
					3 : 4-Dinitroaniline	7·5	0	0	100

Rearrangement in the Presence of Anisole.—2 : 3-Dinitroaniline (17·2 g.) was heated (4·25 hr.) at 110° with concentrated sulphuric acid (40 ml.) and anisole (53 ml.). The mixture was poured on ice, and the solution extracted with ether (extract *A*). The aqueous solution was neutralised with sodium hydroxide and again extracted with ether (extract *B*). Both extracts were dried (Na_2SO_4) and evaporated, and the residues were dissolved in benzene and chromatographed on alumina. Elution with benzene gave the following :

Extract A. (i) A pale yellow substance (0·75 g.) which was not satisfactorily purified, (ii) *N*-methyl-2 : 5-dinitroaniline (0·95 g., 5%), which crystallised from ethanol or *cyclo*hexane

as red needles, m. p. and mixed m. p. 168·5—169° (lit., 163°) (Found : C, 43·0; H, 3·7; N, 21·6. Calc. for $C_7H_7O_4N_3$: C, 42·7; H, 3·6; N, 21·3%), (iii) 2 : 5-dinitroaniline (4·45 g., 26%), m. p. and mixed m. p. 137°, (iv) 2 : 3-dinitroaniline (2·70 g., 16%), m. p. and mixed m. p. 126°, and (v) 3 : 4-dinitroaniline (2·04 g., 12%), m. p. and mixed m. p. 153°.

Extract B. (i) The unidentified substance above (0·17 g.) and (ii) *m*-nitroaniline (1·75 g., 13·5%), m. p. and mixed m. p. 113°.

Hydrolysis of 2 : 3-*Dinitroacetanilide.*—2 : 3-Dinitroacetanilide (5·0 g.) was refluxed (3 hr.) with ethanol (100 ml.) and concentrated hydrochloric acid (20 ml.). After dilution with water, the mixture gave 2 : 3-dinitroaniline (94%), m. p. and mixed m. p. 127°.

Nitration of m-*Nitrophenol.*—*m*-Nitrophenol (80 g.) was nitrated by Sidgwick and Aldous's method (*J.*, 1921, **119**, 1002). The first crops of 2 : 5-dinitrophenol (14 g.; m. p. 105°) and 3 : 4-dinitrophenol (18 g.; m. p. 137°) were separated as suggested by these authors. The residue was chromatographed on silica, with benzene as eluant, and 2 : 5-dinitrophenol (8·0 g.), 2 : 3-dinitrophenol (7·1 g.; m. p. 145°), *m*-nitrophenol (9·0 g.), and 3 : 4-dinitrophenol (16·0 g.) were obtained in that order. Chromatography is more satisfactory than the fractional crystallisation procedure used by Sidgwick and Aldous.

Action of Sulphuric Acid on 2 : 3-, 2 : 5-, *and* 3 : 4-*Dinitrophenol.*—The appropriate compound (3·0 g.) was heated with concentrated sulphuric acid in an ethanol, toluene, or chlorobenzene vapour bath. After the requisite time, the mixture was poured on ice, and the product was filtered off, washed and dried. The filtrate was extracted with ether, the solid obtained on evaporation was combined with the above product, and the mixture was chromatographed on silica in benzene. Table 2 summarises the results.

TABLE 2.

Compound	H_2SO_4 (ml.)	Time (hr.)	Temp.	Yield of dinitrophenol (%) 2 : 3-	2 : 5-	3 : 4-
2 : 3-Dinitrophenol	50	7·5	78°	93	0	0
	30	7·0	112	25	7·5	0
	20	3·0	128	8	6	0
2 : 5-Dinitrophenol	10	5·0	78	0	97	0
	10	4·0	128	0	23	0
3 : 4-Dinitrophenol	10	6·5	78	0	0	100
	10	4·0	128	0	0	87

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UNIVERSITY OF MELBOURNE, VICTORIA, AUSTRALIA. [*Received, December 3rd*, 1954.]

The Influence of Electrolytic Dissociation upon Rates of Reactions. Part I. The Common-ion Effect in the Hydrolysis of tert.-*Butyl Bromide.*

By G. R. NASH and C. B. MONK.

[Reprint Order No. 5951.]

The hydrolysis of *tert.*-butyl bromide in aqueous acetone in the presence of added bromides has been studied. The dissociation constants of hydrobromic acid and the salts used in the kinetic work have been calculated from conductivity measurements, so that the true ionic strengths could be assessed in the hydrolysis studies. In this way a critical examination of Hughes and Ingold's treatment of ionic-strength effects in S_N1 reactions, and of an ion–dipole equation due to Moelwyn-Hughes, has been possible. Both of these approaches account fairly satisfactorily for the observed increasing hydrolysis rates with increasing ionic strengths.

THE dependence of the rates of many chemical reactions upon electrolyte concentrations is expressed satisfactorily by Brønsted's relation. There are, however, a number of examples which cannot be thus accommodated. These include reactions between ions and polar molecules, and for these the theoretical effect of concentration upon the reaction rates is founded upon the polarity of the molecular species, the ion charge, and the ionic

strength of the solution. This is dealt with in detail later. Even when both the reacting species are ions, apparent exceptions to Brønsted's equation have been found, and one reason for this may be that all the electrolytes present are assumed to be completely dissociated. For example, Davies and Wyatt (*Trans. Faraday Soc.*, 1949, **45**, 744) have shown that the anomalous rates of reaction between the thiosulphate and bromoacetate ions when calcium and barium salts are added can be attributed to ion-pair formation. Such effects can be important in ion–dipole reactions. Evans and Sugden, for example (*J.*, 1949, 270), showed that the apparently decreasing value of the bimolecular rate constant for the exchange reaction $RBr + Br^{*-} \rightleftharpoons RBr^{*} + Br^{-}$ (where Br^{*} is radioactive and R is an alkyl group) in acetone in presence of increasing concentrations of lithium bromide is accounted for by incomplete dissociation. When lithium bromide ion-pairs are allowed for, the rate constant is independent of the salt concentration.

As a continuation to such aspects of reaction rates we have studied the hydrolysis of *tert.*-butyl bromide in aqueous acetone, both in the absence and in the presence of added bromide electrolytes. In such solvents, if the proportion of water is small, ion-association can be extensive. Olson and Konecny (*J. Amer. Chem. Soc.*, 1953, **75**, 5801) have given data illustrating this for lithium bromide. This salt was used by Bateman, Hughes, and Ingold (*J.*, 1940, 960) in their studies of the hydrolysis of *tert.*-butyl bromide in aqueous acetone. They found that the first-order rate of hydrolysis in the absence of this salt increases as the reaction proceeds, and the rate constant is much higher when lithium bromide is present. These increases are attributed to an ionic-strength effect, and in the quantitative treatment of this, Bateman, Church, Hughes, Ingold, and Taher (*J.*, 1940, 979) assumed that the inorganic constituents were completely dissociated. Since this appeared doubtful, we have measured the conductivities of hydrobromic acid and of several bromides in aqueous acetone, and from these we have calculated the relevant dissociation constants. These have been used to follow the ionic-strength changes during the hydrolysis of *tert.*-butyl bromide.

Conductivity Measurements.—Dissociation constants in 90% acetone (by vol.) were calculated by Fuoss's method (*J. Amer. Chem. Soc.*, 1935, **57**, 488). The figures are given

TABLE 1. *Conductivity of hydrobromic acid in aqueous acetone.*

90% Acetone

10^4c	Λ	$10^3F(z)/\Lambda$	$10^3c\Delta f^3/F(z)$	10^3K	10^4c	Λ	$10^3F(z)/\Lambda$	$10^3c\Delta f^3/F(z)$	10^3K
				25°, Λ° = 117·1					
1·971	109·5	8·75	1·89	6·5	3·356	106·6	8·88	3·01	6·5
1·975	109·7	8·74	1·89	(7·3)	5·145	103·3	9·04	4·29	6·3
2·940	107·2	8·86	2·68	6·2	6·143	101·8	8·99	4·96	5·9
				30°, Λ° = 125·6					
2·873	115·2	8·25	2·80	6·3	8·490	105·9	8·65	6·82	6·3
3·265	114·3	8·28	3·13	6·25	9·598	104·65	8·70	7·50	6·45
5·252	110·4	8·45	4·65	6·1	10·88	103·2	8·78	8·23	6·5
				35°, Λ° = 134·8 (134·4, Davies's method)					
3·249	122·4	7·72	3·31	6·1	8·821	112·9	8·06	7·34	6·2
3·739	121·15	7·79	3·71	5·9	10·46	110·7	8·16	8·30	6·1
5·459	117·9	7·88	5·14	6·0	10·64	110·5	8·16	8·41	6·1

70% Acetone, 25°, Λ° = 133·1

10^4c	Λ	$\Lambda^{\circ\prime}$	10^4c	Λ	$\Lambda^{\circ\prime}$	10^4c	Λ	$\Lambda^{\circ\prime}$	10^4c	Λ	$\Lambda^{\circ\prime}$
3·191	130·1	133·1	5·278	129·2	133·0	6·725	128·9	133·2	8·765	128·1	133·1
3·709	129·9	133·1	5·755	129·1	133·1	7·553	128·6	133·2	9·672	128·1	133·3

in Table 1, where $F(z) = 1 - z\{1 - z[1 - z(1 \ldots .)^{-\frac{1}{2}}]^{-\frac{1}{2}}\}^{-\frac{1}{2}}$, and $z = \alpha\Lambda_0^{-\frac{3}{2}}(c\Lambda)^{\frac{1}{2}}$, where α is one of the terms of Onsager's conductivity equation

$$\Lambda = \Lambda^\circ - (\alpha\Lambda^\circ + \beta)I^{\frac{1}{2}} = \Lambda^\circ - BI^{\frac{1}{2}}$$

in which I is the ionic strength. Fuoss has tabulated values of $F(z)$ for various values of z. For comparative purposes, Davies's method (*Trans. Faraday Soc.*, 1927, **23**, 351) was also used to calculate the dissociation constants, and these are listed under 10^3K.

In Onsager's equation, $B = 355{\cdot}5$, $379{\cdot}8$, and $401{\cdot}3$ at 25°, 30°, and 35° respectively in 90% acetone, and is $169{\cdot}4$ in 70% acetone. The values of $\Lambda^{\circ\prime}$ in Table 1 were obtained by the addition of $BI^{\frac{1}{2}}$ to Λ; the constancy of $\Lambda^{\circ\prime}$ indicates that dissociation is complete in 70% acetone.

The dissociation data and other calculations were obtained with the help of the following physical constants :

Acetone vol. %	wt. %	Temp.	D	$10^3\eta$	A	Acetone vol. %	wt. %	Temp.	D	$10^3\eta$	A
90	87·5	25°	25·3	4·57	2·787	90	87·5	50°	22·5	—	2·943
90	,,	30	24·6	4·36	2·836	70	64·7	25	38·25	9·40	1·500
90	,,	35	24·1	4·08	2·925						

The dielectric constants D were interpolated from those of Akerlöf (*J. Amer. Chem. Soc.*, 1932, **54**, 4132), and the viscosities (η) from those given in the International Critical Tables (Vol. V, p. 22) and by Olson and Konecny (*loc. cit.*). The factor A refers to the limiting form of the Debye–Hückel activity coefficient expression, $-\log f_i = 1{\cdot}8246 \times 10^6 z^2 I^{\frac{1}{2}}(DT)^{-\frac{3}{2}} = -Az^2I^{\frac{1}{2}}$.

Lithium and Potassium Bromides.—Table 2 contains the measurements and dissociation constants (calculated by Davies's method, *loc. cit.*).

TABLE 2. *Conductivities of lithium and potassium bromides in 90% acetone at 25°.*

				LiBr. $\Lambda^\circ = 101{\cdot}1$, $B = 335{\cdot}5$				
10^4c ...	3·486	5·126	5·904	9·248	13·70	21·61	26·41	38·77
Λ	94·89	90·83	89·95	87·29	83·81	78·72	76·59	71·97
10^3K ...	1·35	1·2	1·25	1·25	1·3	1·15	1·21	1·21
				KBr. $\Lambda^\circ = 115{\cdot}4$, $B = 353{\cdot}5$				
10^4c ...	3·176	4·486	5·144	6·508	6·748	9·218	9·611	11·52	12·43
Λ	107·10	105·30	104·28	102·75	102·40	100·20	99·81	98·40	97·59
10^3k ...	1·3	1·3	1·2	1·25	1·2	1·3	1·25	1·3	1·3

Magnesium Bromide.—On plotting Λ against $c^{\frac{1}{2}}$, a curve was obtained from which a rough estimate of $\Lambda^\circ = 105$ was obtained. On using this in Onsager's equation for a 2 : 1-valent salt, it became apparent that ion-association is considerable in this system and that both of the equilibria (*a*) $MgBr^+ \rightleftharpoons Mg^{2+} + Br^-$ and (*b*) $MgBr_2 \rightleftharpoons MgBr^+ + Br^-$ need considering. By trial and error, $\Lambda^\circ = 108$ gave K' values [where K' is the apparent dissociation constant for process (*a*), it being assumed that process (*b*) can be ignored] which varied linearly with the salt concentration, so this value was used for the final calculations. Assumptions are involved to obtain the limiting ion mobilities. Since Λ° (water) = $131{\cdot}36 = 53{\cdot}06$ for $Mg^{2+} + 78{\cdot}3$ for Br^- (Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold, 1943, p. 172), λ° (Mg^{2+}, 90% acetone) was taken as $53{\cdot}06 \times 108/131{\cdot}4 = 43{\cdot}6$, and similarly $64{\cdot}4$ was taken for the bromide ion. The ion-pair $MgBr^+$ was assigned the value of $43{\cdot}6/2$ on the assumption that its mobility is proportional to that of the ion of like charge. The consequent treatment is as follows. Let α = fraction of $MgBr_2$ dissociated into $MgBr^+$ and Br^-, β = fraction of $MgBr^+$ dissociated into Mg^{2+} and Br^-; then if m is the stoicheiometric molarity,

$$\Lambda\,(\text{obs.}) = (\alpha/2)(1-\beta)\{\lambda_{MgBr^+} + \lambda_{Br^-}\} + \alpha\beta\{\lambda_{Mg^{2+}} + \lambda_{Br^-}\} \quad . \quad . \quad . \quad (1)$$

and

$$I = \alpha m\,(1 + 2\beta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In the more dilute solutions, $\alpha = 1$ can be taken as a first approximation, whence, by using the appropriate Onsager equations,

$$\lambda_{MgBr} + \lambda_{Br^-} = 86{\cdot}2 - 317I^{\frac{1}{2}}, \text{ and } \lambda_{Mg^{2+}} + \lambda_{Br^-} = 108{\cdot}0 - 546I^{\frac{1}{2}}$$

Values of β which will be termed β' can be established, and K_1' calculated where

$$\log K_1' = \log (a_{Mg^{2+}}a_{Br^-})/a_{MgBr^+} = \log\{\beta'\,(1+\beta')m/(1-\beta')\} - 4AI^{\frac{1}{2}}$$

The values of K_1' are given in Table 3, and extrapolation of K_1' against m gave $K_1 = 3{\cdot}1 \times 10^{-4}$. To obtain K_2 for process (*b*), where

$$\log K_2 = \log (a_{MgBr^+} a_{Br^-})/a_{MgBr_2} = \log \{\alpha^2(1 + \beta)(1 - \beta)m/(1 - \alpha)\} - 2AI^{\frac{1}{2}}$$

values of α and β were calculated by approximations using the correct expression for K_1, *i.e.*,

$$\log 3{\cdot}1 \times 10^{-4} = \log \{\alpha\beta\ (1 + \beta)m/(1 - \beta)\} - 4AI^{\frac{1}{2}} \quad . \quad . \quad . \quad (3)$$

and (1) and (2) above. To do this, $\alpha = 1$ was taken, and values of β and I calculated from (1) and (2). Substitution of these in (3) gave a first value of α. This was used in (1) and (2) to give truer values of β and I, and so on until constant α and β values were established. The results are given in Tables 3 and 4.

TABLE 3. *Conductivity of magnesium bromide in 90% acetone at 25°.*

10^4c	A	$10\beta'$	$10^4K_1'$	10^4c	A	$10\beta'$	$10^4K_1'$	10^4c	A	$10\beta'$	$10^4K_1'$
4·561	72·08	5·77	2·78	7·486	64·61	4·59	2·38	13·36	55·95	3·50	2·05
4·875	70·86	5·58	2·68	8·023	63·56	4·59	2·44	14·15	55·30	3·43	2·04
6·224	67·29	5·10	2·57	10·37	59·55	4·01	2·22	17·55	52·55	3·06	1·92
7·443	64·69	4·75	2·48	11·02	58·85	3·93	2·22	18·58	51·55	2·90	1·84

TABLE 4. *Calculation of K_2 for magnesium bromide.*

10^4c	11·02	13·36	14·15	17·55	18·58
10α	9·30	9·13	9·14	9·03	8·92
10β	4·80	4·56	4·47	4·23	4·20
10^3K_2	3·5	3·3	3·5	3·7	3·4

Hydrolysis Measurements.—Bateman, Hughes, and Ingold's procedure (*loc. cit.*) was used to follow the rate of hydrolysis of *tert.*-butyl bromide in 90% acetone at 25°, *i.e.*, by measuring the acid liberated. These workers found that the reversibility of the reaction was below the limit of measurement, the proportion of acid formed being at least 99·8%. As a check, we measured the conductivity of a mixture of *tert.*-butyl alcohol and hydrobromic acid in the solvent. No change of the bridge reading over a period of 24 hr. was observed, confirming that the back reaction is negligible. The usual integrated form of the first-order velocity constant expression was used to calculate k_1, $k_1t = 2{\cdot}303 \log (a - a_0)/(a_0 - x)$, where a_0 = initial titre, a = titre for complete hydrolysis, x = titre at time t. In Table 5, m = stoicheiometric molarity of acid at time t, and k_1 is related to the time in secs. Only a few specimen runs are given. Others are given in the graph, and the average slopes and values of k_1° (k_1 at zero ionic strength) are given in Table 7.

TABLE 5. *Hydrolysis of* tert.*-butyl bromide in 90% acetone at 25°.*

Initial Bu^tBr = 0·1039 (data of Bateman, Hughes, and Ingold, *loc. cit.*).

Hrs.	3·15	4·10	6·20	8·20	10·0	13·5	18·3	26·0	30·8	37·3	43·8
10^3m	1·42	1·81	2·63	3·38	4·00	5·10	6·86	7·69	8·32	8·97	9·38
10^3I	0·95	1·17	1·62	2·02	2·33	2·89	3·77	4·18	4·50	4·85	5·03
10^3k_1	1·30	1·30	1·31	1·34	1·36	1·40	1·44	1·45	1·47	1·49	1·50

Initial Bu^tBr = 0·1105, initial HBr = 0·0533

Hrs.	6·26	8·25	10·33	12·25	14·17	23·17	26·17	28·33	30·67
10^3m	8·61	9·47	10·23	10·85	11·49	13·57	14·04	14·36	14·63
10^3I	4·65	5·08	5·48	5·76	6·07	7·11	7·34	7·50	7·63
10^3k_1	1·56	1·58	1·57	1·57	1·60	1·64	1·65	1·67	1·67

Initial Bu^tBr = 0·1103, initial LiBr = 0·0463

Hrs.	4·00	6·00	8·00	10·0	12·0	14·0	26·0	30·0
10^3m	2·20	3·23	4·07	4·83	5·55	6·20	8·72	9·24
10^3I	4·40	4·89	5·34	5·73	6·09	6·42	7·68	7·80
10^3k_1	1·54	1·60	1·60	1·60	1·62	1·64	1·67	1·68

Initial Bu^tBr = 0·1000, initial $MgBr_2$ = 0·0152

Hrs.	4·00	6·00	8·0	10·25	12·0	14·0	23·4	28·25	30·25
10^3m	1·91	2·74	3·51	4·28	4·81	5·37	7·40	8·07	8·29
10^3I	2·4	2·9	3·3	3·7	4·1	4·2	5·4	5·6	5·9
10^3k_1	1·47	1·48	1·50	1·51	1·52	1·53	1·60	1·62	1·62

The ionic strengths I in Table 5 were calculated after making allowance for the ion-pair concentrations. These were obtained by approximations from the relevant expressions such as

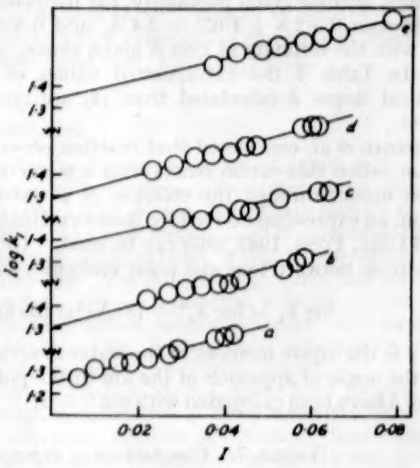
$$\log [MBr] = \log [M^+][Br^-] - \log K - 2F(I)$$

where $M^+ = H^+$, K^+, or Li^+, $I = [Br^-]$, and

$$F(I) = -\log f_i = Az_i^2\{I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0{\cdot}2I\}$$

The activity coefficient expression is based on that of Davies (*J.*, 1938, 2093), which is satisfactory in aqueous solutions up to $I = 0{\cdot}1$. The values of A have been given on p. 1901.

(*a*) 0·1056M-Bu^{t}Br.
(*b*) 0·0991M-Bu^{t}Br, 0·0271M-HBr.
(*c*) 0·1150M-Bu^{t}Br, 0·0240M-LiBr.
(*d*) 0·1070M-Bu^{t}Br, 0·0231M-KBr.
(*e*) 0·1278M-Bu^{t}Br, 0·0404M-KBr.



Discussion

The average dissociation constants obtained from the conductivity data are collected together in Table 6. Olson and Konecny (*loc. cit.*) obtained 0·0095 and 0·0091 for lithium bromide in 90% acetone at 25° and 35° respectively, by using Fuoss's method (*loc. cit.*).

According to Hughes, Ingold, and their collaborators the mechanism of hydrolysis may be represented as follows:

$$Bu^tBr \underset{2}{\overset{1}{\rightleftharpoons}} Br^- + Bu^{t+}$$

$$Bu^{t+} + H_2O \xrightarrow{3} Bu^tOH + H^+ \qquad (S_N1)$$

$$Bu^{t+} \xrightarrow{3'} \textit{iso}Butylene + H^+ \qquad (E1)$$

The quantitative treatment developed by Bateman, Church, Hughes, Ingold, and Taher (*loc. cit.*) to account for the changing rates of unimolecular hydrolysis rate constants as the reaction proceeds, or in the presence of added electrolytes, is founded upon the

Table 6. *Average dissociation constants* ($\times 10^3$).

Temp.	HBr	LiBr	KBr	$MgBr_2$
25°	6·3	12·0	13·0	0·31 (K_1), 3·5 (K_2)
30	6·2	—	—	—
35	6·1	—	—	—
50	6·0 *	10·0$_5$ *	—	

* Estimated.

assumption that the measured rate constant is the rate constant for ionisation (designated as 1 above), and the ionic strength influences the extent of Bu^{t}Br ionisation. The Bu^{t}Br

molecule is assumed to pass through a transition state where it consists, in effect, of two point charges $\pm z\epsilon$ separated by a fixed distance d. The developed equation is

$$\log k_1 = \log k_1^\circ + 0{\cdot}912 \times 10^{16} z^2 dI/(D^2T^2) = \log k_1^\circ + \phi I \quad . \quad . \quad (4)$$

where k_1° is the rate constant at $I = 0$. The magnitude of the parameter $\sigma = z^2d$ is not known exactly. It is assumed that in the transition state half an electron is transferred from the alkyl group to the bromine atom, *i.e.*, $z^2 = 0{\cdot}25$. It was estimated from the Morse potential-energy function that d is about 2·59 Å, the energy of activation used being that found from the solvolysis rates in 80% ethanol. Franklin (*Trans. Faraday Soc.*, 1952, **48**, 441) calculated the radius of the Bu^{t+} ion to be 2·8 Å. The crystallographic radius of the Br^- ion is 1·95 Å, and from Stokes's law and the estimated limiting ion mobility of the Br^- ion in 90% acetone given previously, the hydrated Br^- radius is 2·8 Å. These figures give d as between $0{\cdot}5(2{\cdot}8 + 1{\cdot}95) = 2{\cdot}4$ Å, and $0{\cdot}5(2{\cdot}8 + 2{\cdot}8) = 2{\cdot}8$ Å. The mean of 2·6 Å agrees with the estimate of 2·59 Å given above, but is subject to an uncertainty of nearly 10%. In Table 7 the extrapolated values of k_1°, the experimental slopes, and the theoretical slopes ϕ calculated from (4) are given. Some data from other sources are included.

Bateman *et al.* considered that reaction occurs through collapse of the highly solvated Bu^{t+} ion, when this cation reacts with a water molecule. If, instead, we consider that reaction occurs through the collision of a water molecule of sufficient energy with the Bu^{t+} ion, an expression derived by Moelwyn-Hughes ("Kinetics of Reactions in Solutions," Oxford Univ. Press, 1947, 985) can be used. This expression, which relates rate constants for reactions between ions and polar molecules with the ionic strength, is

$$\log k_1 = \log k_1^\circ + (8\pi N\epsilon^3\mu z \cos\theta)/2303(DkT)^2 = \log k_1^\circ + \delta I$$

where μ is the dipole moment of the water molecule (1·85 D), z the valency of the Bu^{t+} ion, and θ the angle of approach of the ion to the polar axis of the molecule. In Table 7, the value of δ have been calculated with $\cos\theta = 1$.

TABLE 7. *Comparison of experimental and calculated slopes.*

Solute	Solvent	Temp.	$10^5 k_1^\circ$	Electrolyte added (m)	Exptl. slope	ϕ	δ	Ref.
Bu^tBr	90% Acetone	25°	1·25 ± 0·02	—	1·65 ± 0·15	1·04	1·26	Table 5
,,	,,	,,	1·24 ± 0·02	—	1·65 ± 0·15	,,	,,	,,
,,	,,	,,	1·30 ± 0·03	0·027 HBr	1·65 ± 0·2	,,	,,	,,
,,	,,	,,	1·39 ± 0·03	0·053 HBr	1·05 ± 0·2	,,	,,	,,
,,	,,	,,	1·36 ± 0·03	0·024 LiBr	1·2 ± 0·2	,,	,,	,,
,,	,,	,,	1·42 ± 0·04	0·046 LiBr	0·9 ± 0·1	,,	,,	,,
,,	,,	,,	1·29 ± 0·02	0·023 KBr	1·7 ± 0·15	,,	,,	,,
,,	,,	,,	1·34 ± 0·03	0·040 KBr	1·3 ± 0·1	,,	,,	,,
,,	,,	,,	1·35 ± 0·02	0·015 $MgBr_2$	1·4 ± 0·15	,,	,,	,,
,,	,,	50	18·2 ± 0·4	—	1·85 ± 0·15	1·12	1·36	Table 6
,,	,,	,,	~25	0·106 LiBr	~0·6	,,	,,	,,
,,	70% Acetone	,,	51·1 ± 0·4	—	0·39 ± 0·02	0·41	0·54	*a*
,,	80% Ethanol	25	35·6 ± 0·2	—	0·33 ± 0·03	0·52	0·63	*b*
Am^tCl	,,	,,	1·50	—	nil	0·29	0·35	*c*
Am^tBr	,,	,,	55·5 ± 1·0	—	0·6 ± 0·1	,,	,,	*c*
Am^tI	,,	,,	157 ± 3	—	0·8 ± 0·1	,,	,,	*c*
Bu^tBr	60% Dioxan	10	29·0 ± 0·3	—	(0·55)	0·90	1·1	*b*
Bu^tNO_3	85% ,,	25	3·34	—	(1·0)	10·4	12·6	*d*

References: (*a*) Bateman, Hughes, and Ingold, *loc. cit.* (*b*) Benfey, Hughes, and Ingold, *J.*, 1952, 2494. (*c*) Hughes and MacNulty, *J.*, 1937, 1283. (*d*) Lucas and Hammett, *J. Amer. Chem. Soc.*, 1942, **64**, 1928.

Taking the results as a whole, there is broad agreement between the experimental slopes and those calculated by both of the above treatments. For the results in 90% acetone at 25°, which has been studied in the most detail, Moelwyn-Hughes's treatment is in better agreement with experiment than is that of Hughes and Ingold. On the other hand, we have taken $\cos\theta = 1$, which gives the highest values of δ, and we have no means of

deciding if this value of θ is justified. Again, with Hughes and Ingold's expression, a slightly higher value of d would effect closer agreement with the average experimental slope.

There is an experimental factor which makes too rigid a comparison difficult. This originates in what may be called the zero-time error. A small period of time is allowed for temperature equilibrium to be reached, and although the corresponding titration is subtracted from those obtained during an actual run, any resulting error has a considerable influence upon the initial values of k_1, and hence upon the evaluated slopes of log k_1 against I.

A more critical evaluation of ion–dipole interactions could be obtained by using solvents of very low dielectric constants such as we have with the last example in Table 7, where ϕ and δ are large. Unfortunately, the experimental results for this cannot yet be analysed since the dissociation constant of nitric acid in 85% dioxan is unknown. It is undoubtedly small, since, *e.g.*, hydrochloric acid has a dissociation constant of 0·0002 in 82% dioxan at 25° (Owen and Waters, *J. Amer. Chem. Soc.*, 1938, **60**, 2371).

Experimental

The conductivity equipment has been described by Davies and Monk (*J.*, 1949, 413). The hydrolyses were carried out in a Pyrex flask fitted with a tightly fitting ground-glass stopper, kept at 25° ± 0·01°. The solvent was introduced at least 30 min. before introduction of the *tert.*-butyl bromide, which was meanwhile distilled from a bulk sample, and the amount added to the hydrolysis flask was found by weight. Two min. after addition, a sample was withdrawn for an "initial" titre, and this was regarded as zero time. For the "infinity" titres, four samples were sealed in tubes and kept at 80—90° for a day. For each titration, a 10 ml. sample was pipetted into 100 ml. of ice-cold acetone, and titrated against sodium hydroxide, with lacmoid as indicator (Bateman, Hughes, and Ingold, *loc. cit.*). The infinity titres agreed with those calculated from the amount of *tert.*-butyl bromide weighed out to within ±0·2%.

Lithium bromide was twice recrystallised from absolute alcohol, then dried to constant weight by heating at 300°. "AnalaR" potassium bromide was dried similarly. A stock solution of magnesium bromide was made by refluxing a solution of "AnalaR" hydrobromic acid and excess of magnesium oxide. The concentration of this, and of a stock solution of hydrobromic acid, was found (±0·02%) by gravimetric determination of bromide.

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The Edward Davies Chemical Laboratories,
University College of Wales, Aberystwyth. [*Received, December 10th*, 1954.]

*A General Treatment of the Solvent Extraction of Inorganic Compounds.**

By H. Irving, F. J. C. Rossotti, and R. J. P. Williams.

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A comprehensive treatment of partition equilibria in inorganic systems can be given by combining the concept of step-equilibrium with that of the Nernst partition isotherm. A general relation has been derived between the average composition of the species in each phase. Partial differentiation of this equation with respect to the concentration variables of the system provides a method for determining the relative degrees of association in each phase of metal ions with hydrogen ions and with ligand ions. Its applications in deriving values for the partition coefficients and stability constants of species present in simple "ideal" systems, and in deducing the probable nature of species present in more complicated systems, are outlined. It is shown how the species extracted into the organic phase may occur in the aqueous phase as an insignificant fraction of the total metal present there.

In "non-ideal" systems, changes in the mutual miscibility of aqueous and organic phases brought about by the addition of mineral acids or salts are shown to influence distribution ratios through changes in partition coefficients and stability constants, and to affect the percentage of extraction through these two factors as well as through changes in the ratio of the volumes of the two phases.

Retrograde extraction leading to a maximum in the percentage of extraction is explained, and factors influencing the relative efficiencies of different organic solvents as extracting agencies, and those influencing the relative extractability of different metallic compounds, are discussed.

The solvent extraction of inorganic compounds embraces such diversified observations (cf. Irving, *Quart. Reviews*, **1951**, **5**, 200, and refs. therein) that a generalised quantitative treatment might appear to be impossible. The types of compounds which undergo extraction into organic solvents may be classified broadly into four categories, *viz.*: (i) covalent compounds, such as the halogens, sulphur dioxide, osmium tetroxide (cf. Friedman, *J. Amer. Chem. Soc.*, **1954**, **76**, 3294); (ii) inner complexes of metals with reagents such as dithizone, cupferron, 8-hydroxyquinoline, and acetylacetone; (iii) the mineral acids, their salts, and metal acido-complexes; and (iv) certain salts or ion-pairs which incorporate bulky anions or cations, *e.g.*, tetraphenylarsonium per-rhenate or pertechnetate, salts of cuprous bis-2 : 9-dimethyl-1 : 10-phenanthroline, or ferrous tris-1 : 10-phenanthroline in association with long-chain alkyl sulphates or sulphonates (Friedman and Haugen, *ibid.*, **1954**, **76**, 2060; Powell and Taylor, *Chem. and Ind.*, **1954**, 726).

Quantitative treatments of various degrees of elaboration have been applied to representative examples of each of these classes, but since systems allocated to one or other class seem superficially to have so few features in common, no general treatment has hitherto been considered. In the first part of this paper it is shown that existing ideas can be integrated by combing the concept of step-equilibrium (Bjerrum, "Metal Ammine Formation in Aqueous Solution," Haase, Copenhagen, 1941) with the original treatment of partition equilibrium by Nernst (*Z. physikal. Chem.*, **1891**, **8**, 110). In the second part certain additional complexities, especially in systems of type (iii), which arise from changes in partition coefficients and stability constants in consequence of modifications in phase compositions, are discussed in some detail. Further papers, published concurrently (see footnote,*) describe the application of these ideas to experimental studies of the solvent extraction of ferric chloride and indium halides.

To illustrate the mathematical approach, consider the partition of a solute X. By the

* This is to be regarded as Part I of a group of related papers of which Part II (Chalkley and Williams), and Parts III, IV, and V (Irving and Rossotti) are the four following papers.

Nernst partition law $[X]_o = p[X]$, where the subscript o is used to distinguish a species in the organic phase. If X is polymerised (virtually completely) in the organic phase to a species X_n which is not itself partitioned, we have $[X_n]_o = K[X]_o^n$. Then since $[X_n]_o \gg [X]_o$, the distribution ratio is given by

$$q = \frac{[X]_o + n[X_n]_o}{[X]} = \frac{nK[X]_o^n}{[X]} = nKp[X]^{n-1}$$

whence d log q/d log $[X] = n - 1$. If, then, the gradient of the double logarithmic plot of experimental values of q and $[X]$ is constant and integral, this will establish the validity of the simplifying assumptions and furnish the precise degree of polymerisation of X in the organic phase. However, with inorganic systems the species which undergoes partition may only be a minor component of a complex system in equilibrium; polymerisation may occur in either or both of the phases; and more than one substance may undergo partition simultaneously. Although the equations describing such behaviour (given below) must necessarily be more complicated, their resemblance to the foregoing will be apparent, and the behaviour of their (partial) derivatives will be shown to provide a great deal of detailed information concerning the species which take part in the complex equilibria.

We shall first examine the equilibria existing between the simple ions and all the complex species in a system of two relatively immiscible liquid phases. Such equilibria can be described quantitatively in terms of step-equilibria governing the relative concentrations of different species in the aqueous phase, and a series of partition coefficients referring to the relative concentrations of the species which are common to the two phases. Clearly, the proposed treatment does not exclude the possibility of step-equilibria between species in the organic phase. But it is impossible to infer from measurements of distribution ratios at equilibrium whether a particular species identified in the organic phase has crossed the phase boundary as such, or has been formed *in situ* by the interaction of two or more species in the organic phase which are in partition equilibrium with corresponding species in the aqueous phase.

General Treatment of Solvent Extraction in Ideal Systems.—Consider an aqueous solution saturated with organic solvent, S, containing metal ions, M^{+r}, hydrogen ions, H^+, and anions, $L^{-\lambda}$, in a medium of constant strength. Assuming the concentration of acid and anion to be such that hydrolysis of any kationic species can be neglected, all the (solvated) complex ions ML_n, the acido-species H_hML_n, and any polynuclear species such as M_2L_6 or $H_2M_3L_{12}$ which might exist in step-equilibria can be represented by a general term $H_hM_mL_n(H_2O)_wS_s$, and their concentrations related to those of the simplest ions by a series of overall stoicheiometric equilibrium constants defined as follows

$$\beta_{hmnws} = H_hM_mL_n(H_2O)_wS_s/[H]^h[M]^m[L]^n[H_2O]^w[S]^s \quad . \quad . \quad . \quad . \quad (1)$$

Here and subsequently charges on the various species will be omitted unless they are specially relevant to the discussion. For purposes of definition no distinction need be drawn between different types of complexes, *e.g.*, between normal or " robust " complexes (cf. Bjerrum, *op. cit.*, p. 81) and weaker ion-pair aggregates. Stoicheiometric partition coefficients for each possible species are defined by

$$p_{hmnws} = [H_hM_mL_n(H_2O)_wS_s]_o/[H_hM_mL_n(H_2O)_wS_s] \quad . \quad . \quad . \quad . \quad (2)$$

where the subscript o is used to distinguish the organic phase from the aqueous phase. We can now write a general expression for the distribution ratio

$$q = \frac{\text{total concn. of metal in the organic phase}}{\text{total concn. of metal in the aqueous phase}}$$

$$= \frac{\Sigma m[H_hM_mL_n(H_2O)_wS_s]_o}{\Sigma m[H_hM_mL_n(H_2O)_wS_s]} =$$

$$= \frac{\Sigma p_{hmnws}\,\beta_{hmnws}\,m\,[H]^h[M]^m[L]^n[H_2O]^w[S]^s}{\Sigma\beta_{hmnws}\,m\,[H]^h[M]^m[L]^n[H_2O]^w[S]^s} \quad . \quad . \quad . \quad . \quad (3)$$

where the summation includes all physically significant combinations of h, m, n, w, and s. Equation (3) can immediately be simplified by excluding terms from the numerator for which $p_{hmnws} = 0$. Moreover, considerations of electroneutrality exclude the partition of charged species and impose the condition $m\nu + h = n\lambda$. However complex, or however numerous, the different species in the aqueous phase may be, their average composition can be represented by a single symbol, *viz.*, $H_{\bar{m}\bar{h}}M_{\bar{m}}L_{\bar{m}\bar{n}}(H_2O)_{\bar{m}\bar{w}}S_{\bar{m}\bar{s}}$, where $\bar{m}$ represent the "polymerisation number," *i.e.*, the average number of metal atoms per molecular species, and $\bar{h}$ and $\bar{n}$ the average number of hydrogen and ligand atoms, and $\bar{w}$ and $\bar{s}$ the average number of molecules of water and of organic solvent attached per atom of metal. These definitions correspond exactly with the concept, originally introduced by Bjerrum (*op. cit.*), of the "degree of formation" (also termed the "ligand number" by other authors) of the simpler system of mononuclear complexes representable by the formula ML_n ($n = 0, 1, \ldots . N$). Equation (3) can now be rewritten in the form

$$q = \overline{\mathbf{m}}[H_{\overline{\mathbf{m}}\overline{\mathbf{h}}}M_{\overline{\mathbf{m}}}L_{\overline{\mathbf{m}}\overline{\mathbf{n}}}(H_2O)_{\overline{\mathbf{m}}\overline{\mathbf{w}}}S_{\overline{\mathbf{m}}\overline{\mathbf{s}}}]_o/\overline{m}[H_{\bar{m}\bar{h}}M_{\bar{m}}L_{\bar{m}\bar{n}}(H_2O)_{\bar{m}\bar{w}}S_{\bar{m}\bar{s}}]$$
$$= \frac{\overline{\mathbf{pm}}\overline{\boldsymbol{\beta}}[H]^{\overline{\mathbf{m}}\overline{\mathbf{h}}}[M]^{\overline{\mathbf{m}}}[L]^{\overline{\mathbf{m}}\overline{\mathbf{n}}}[H_2O]^{\overline{\mathbf{m}}\overline{\mathbf{w}}}[S]^{\overline{\mathbf{m}}\overline{\mathbf{s}}}}{\overline{m}\beta[H]^{\bar{m}\bar{h}}[M]^{\bar{m}}[L]^{\bar{m}\bar{n}}[H_2O]^{\bar{m}\bar{w}}[S]^{\bar{m}\bar{s}}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Since the ligand numbers will not, in general, be identical in the two phases, those in the organic phase are distinguished by heavy (Clarendon) type, while italic subscripts refer to the aqueous phase. The partition coefficient and overall stability constant of the (average) species in the organic phase, $H_{\overline{\mathbf{m}}\overline{\mathbf{h}}}M_{\overline{\mathbf{m}}}L_{\overline{\mathbf{m}}\overline{\mathbf{n}}}(H_2O)_{\overline{\mathbf{m}}\overline{\mathbf{w}}}S_{\overline{\mathbf{m}}\overline{\mathbf{s}}}$, as defined by equations (2) and (1) are $p_{\overline{\mathbf{m}}\overline{\mathbf{h}},\overline{\mathbf{m}},\overline{\mathbf{m}}\overline{\mathbf{n}},\overline{\mathbf{m}}\overline{\mathbf{w}},\overline{\mathbf{m}}\overline{\mathbf{s}}}$ and $\beta_{\overline{\mathbf{m}}\overline{\mathbf{h}},\overline{\mathbf{m}},\overline{\mathbf{m}}\overline{\mathbf{n}},\overline{\mathbf{m}}\overline{\mathbf{w}},\overline{\mathbf{m}}\overline{\mathbf{s}}}$, and are abbreviated to $\overline{\mathbf{p}}$ and $\overline{\boldsymbol{\beta}}$; the stability constant for the (average) species in the aqueous phase is $\beta_{\bar{m}\bar{h},\bar{m},\bar{m}\bar{n},\bar{m}\bar{w},\bar{m}\bar{s}}$ and is abbreviated to $\bar{\beta}$. Taking logarithms, we have

$$\log q = \log(\overline{\mathbf{p}}\overline{\boldsymbol{\beta}}/\bar{\beta}) + \log(\overline{\mathbf{m}}/\overline{m}) + (\overline{\mathbf{mh}} - \overline{m}\bar{h}) \log [H]$$
$$+ (\overline{\mathbf{m}} - \overline{m}) \log [M] + (\overline{\mathbf{mn}} - \overline{mn}) \log [L]$$
$$+ (\overline{\mathbf{mw}} - \overline{mw}) \log [H_2O] + (\overline{\mathbf{ms}} - \overline{ms}) \log [S] \quad . \quad . \quad . \quad (5)$$

At this stage it will be convenient to develop the argument with reference to what may arbitrarily be distinguished as "ideal" and "non-ideal" systems. Systems are termed ideal if, over the whole range of conditions analytically accessible, there are no changes (*a*) in the solvent properties of the two phases, and (*b*) in the extent of solvation (by water and/or molecules of organic solvent) of any species in either phase. Under such conditions the stoicheiometric stability constants $\overline{\boldsymbol{\beta}}$ and $\bar{\beta}$, the partition coefficient $\overline{\mathbf{p}}$, and the ligand numbers $\overline{\mathbf{w}}$, $\overline{w}$, and $\bar{s}$, $\bar{s}$ are constant. If the ionic strength is controlled and [S] and $[H_2O]_o$ are constant, the last two terms in equation (5) may be assimilated into the first term, giving

$$\log q = A + \log (\overline{\mathbf{m}}/\overline{m}) + (\overline{\mathbf{mh}} - \overline{m}\bar{h}) \log [H]$$
$$+ (\overline{\mathbf{m}} - \overline{m}) \log [M] + (\overline{\mathbf{mn}} - \overline{mn}) \log [L] \quad . \quad . \quad . \quad (5a)$$

where the term A is independent of [H], [M], and [L] and can be eliminated by differentiation (see p. 1909). In non-ideal systems changes in one or other of the variables C_H, C_M, C_L, or C_{HL} (see p. 1915) bring about changes in the mutual miscibility of the phases. The various consequences of the concomitant changes in phase composition, stability constants, and partition coefficients are explored in the second section of this paper.

Solvent Extraction in Ideal Systems.—In principle, values of h, m, and n, for each complex species which exists in either phase, and the corresponding stability constants and partition coefficients can be calculated from a sufficiently large number of measurements of the distribution ratio, q, for known values of $[H^+]$, [M], and [L]. The free hydrogen-ion concentration can often be obtained from measurements of pH, but in general only the total concentration of metal, C_M, and the total ligand concentration, C_L, can be determined analytically in the two phases. However, by using radioactive metal ions in tracer concentrations it is often possible to ensure that $C_L \gg \Sigma n[H_hM_mL_n]$ and that $C_H \gg \Sigma h[H_hM_mL_n]$ so that the approximations $[L] \cong C_L$ and $[H^+] \cong C_H$ are justified. Examples

of this device appear in Parts III—V. So far no one has attempted to measure [M] or [L] directly in solvent extraction studies, doubtless owing to the uncertainties introduced by junction potentials. Having determined the distribution ratio, q, for known values of C_H, C_M, and C_L, covering as wide a range as possible, the results can best be evaluated by considering the partial derivatives of equation (5*a*).

(a) *Variations in metal concentration.* By partial differentiation of equation (5*a*) with respect to the concentration of free metal ions we have

$$(\partial \log q/\partial \log [M])_{[H],[L]} = (\bar{\mathbf{m}} - \bar{m}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Thus when the extent of polymerisation of the metal complexes is the same in each phase, the value of this derivative is zero. In the limiting case, as the concentration of free metal ions, [M], tends to zero, $\bar{m}$ tends to unity, so that a zero value of the derivative at low metal concentrations signifies that all the species are mononuclear. Positive values of $\partial \log q/\partial \log [M]$ indicate that the degree of polymerisation is greater in the organic phase ($\bar{\mathbf{m}} > \bar{m}$), while negative values indicate that it is greater in the aqueous phase ($\bar{\mathbf{m}} < \bar{m}$). Although the value of the derivative $\partial \log q/\partial \log [M]$ at a particular concentration of free hydrogen ion and free ligand ion provides a useful index of the relative association of metal in the two phases, it clearly affords no further information concerning the nature of the species in the organic phase, or, indeed, of the nature of the species which may be polymerising. However, if the composition of the species extracted into the organic phase is already known, deductions concerning the polymerised species may be made by investigating the way in which the value of the derivative (6) depends on the parameters [H] and [L]. A particular illustration of this type of treatment appears in Part IV of this series. If it is impossible to neglect hydroxy-complexes in setting up a general equation of type (3), an obvious extension provides a method of studying polynuclear hydrolysis products (cf. Connick and Reas, *J. Amer. Chem. Soc.*, 1951, **73**, 1171). Indeed any type of competitive complex formation can be studied.

Examples of every type of behaviour predicted by equation (6) have been realised in practice. In the extraction of most inner complexes with organic reagents, mononuclear species appear to predominate in both phases. Association in the organic layer has been postulated in the extraction of ferric, gallium, and auric chlorides from hydrochloric acid (Nachtrieb and Conway, *ibid.*, 1948, **70**, 3547; Nachtrieb and Fryxell, *ibid.*, 1949, **71**, 4035; Haas, Thesis, Chicago, 1950), and the formation of a dinuclear species in the aqueous phase (which undergoes partition to a negligible extent) appears to be the reason for the decreasing extraction of indium from hydrobromic acid into *iso*butyl methyl ketone as the metal concentration increases (Irving and Rossotti, Part IV).

A plot of experimental values of log q against log C_M gives values of the partial derivative $(\partial \log q/\partial \log C_M)_{[H],[L]}$ which can readily be shown to be identical with those of the partial derivative $\partial \log q/\partial \log [M]$ for the case where $\bar{\mathbf{m}} = \bar{m}$. But in the general case, and where the phases at equilibrium have the same volume,

$$\partial \log q/\partial \log C_M = (\bar{\mathbf{m}} - \bar{m})(1 + q)/(\bar{\mathbf{m}} + \bar{m}q) \quad . \quad . \quad . \quad (6a)$$

Introducing the identity, E (percentage extraction) $= 100q/(1 + q)$, valid for equal phase volumes, we obtain an equivalent expression

$$\partial \log E/\partial \log C_M = (\bar{\mathbf{m}} - \bar{m})/(\bar{\mathbf{m}} + \bar{m}q) \quad . \quad . \quad . \quad . \quad . \quad (6b)$$

(b) *Variations in free ligand concentration.* At constant metal and hydrogen-ion concentration we have

$$(\partial \log q/\partial \log [L])_{[H],[M]} = \bar{\mathbf{m}}\bar{\mathbf{n}} - \bar{m}\bar{n} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The condition [M] = constant is difficult to realise where polynuclear species contribute appreciably to the equilibria, and the potentialities of metal buffers for studies of solvent extraction have not yet been exploited.

In the most favourable case, where only mononuclear species are present in either phase and a single complex of composition H_hML_n is extracted into the organic phase, $\bar{\mathbf{m}} = \bar{m} = 1$,

and $\bar{n}$ is simply the customary " degree of formation " of the aqueous system of complexes. Equation (7) now reduces to the form

$$\partial \log q/\partial \log [L] = \bar{\mathbf{n}} - \bar{n} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7a)$$

A particular case of this equation, in the form $\bar{n} = \mathbf{4} + \mathrm{d}(\log q)/\mathrm{d}(\mathrm{pAa})$, was derived by Rydberg in 1950 (*Acta Chem. Scand.*, **1950**, **4**, 1503) and shown to apply to the extraction of the neutral thorium complex $ThAa_4$ from solutions of Th^{4+} and acetylacetone, HAa.

From the plot of $\log q$ against $\mathrm{pL} = -\log_{10}[L]$, a series of values of $\bar{n}$ can be calculated by equation (7*a*) if the value of $\bar{\mathbf{n}}$ is known or assumed. From the derived formation curve (the plot of $\bar{n}$ against pL) it is possible to calculate values for the individual stability constants, K_1, K_2, ... K_n defining the metal–ligand equilibria (Irving and Rossotti, *J.*, 1954, 2904, and refs. therein) though the accuracy of the data derived from partition measurements only justifies the evaluation of all the constants in favourable cases (cf. Rydberg, *loc. cit.*). A two-parameter equation developed by Dyrssen and Sillén (*Acta Chem. Scand.*, 1953, **7**, 663) facilitates the calculation of a series of equilibrium constants which satisfy the quite arbitrary condition $K_n/K_{n+1} = \text{constant}$; the calculations are, however, exact when $n = 1$ or 2. It should be emphasised that all these approximate conditions assume implicitly that $\bar{\mathbf{n}}$ is known and constant, and that $\bar{\mathbf{m}} = \bar{m} = 1$. In the general case only the difference between the ligand numbers $\bar{\mathbf{m}}\bar{\mathbf{n}}$ and $\bar{m}\bar{n}$ can be determined experimentally from equation (7).

(c) *Variations in hydrogen-ion concentration.* By partial differentiation of equation (5) we have

$$(\partial \log q/\partial \log [H])_{[M],[L]} = (\bar{\mathbf{m}}\bar{\mathbf{h}} - \bar{m}\bar{h}) \quad . \quad . \quad . \quad . \quad . \quad (8)$$

so that if the values of $\bar{\mathbf{m}}$ and $\bar{m}$ are known, the relative extent of association of hydrogen to metal in each case can be determined. Where $\bar{\mathbf{m}} = \bar{m} = 1$, the partial derivative of (8) can be replaced by the more conveniently measurable $(\partial \log q/\partial \log [H])_{C_M[L]}$. The more general case is approached from a different angle on p. 1913. If a non-acidic species, ML_n, represents the composition of the organic phase, values of equation (8) will be zero provided $\bar{\mathbf{h}} = 0$ as well; this condition is usually met for solutions of mineral salts in moderate concentrations of mineral acids. Positive values of the derivative (8) will then correspond to the extraction of acido-species. However, negative values are also feasible at high acidities if, *e.g.*, a non-acidic species were to partition, while $\bar{h} > 0$ owing to the presence in the aqueous phase of an acido-species of low or negligible partition coefficient.

In the extraction of inner complexes, the chelating agent $H_\lambda L$ is usually a weak acid. If monobasic, then $[HL]/[H^+][L^-] = \beta_{101}$, and $[HL]_o/[HL] = p_{101}$ from equations (1) and (2). Where only mononuclear complexes containing no additional hydrogen atoms are concerned $\bar{\mathbf{m}} = \bar{m} = 1$, and $\bar{\mathbf{h}} = \bar{h} = 0$. Eliminating [L] from equation (5*a*), we have

$$\log q = A + (\bar{\mathbf{n}} - \bar{n})\{\log [HL]_o + \mathrm{pH} - \log \beta_{101}p_{101}\} \quad . \quad . \quad . \quad (9)$$

If a single uncharged complex of composition ML_n is extracted, the gradient of the plot of experimental values of $\log q$ against pH (the concentration of reagent in the organic phase being kept constant), or against $\log [HL]_o$ (measured at constant pH), should be $(\bar{\mathbf{n}} - \bar{n})$, where $\bar{n}$, as before, is the degree of formation of the system of complexes in the aqueous phase. The limiting value of equation (9) as $\bar{n}$ tends to zero is given by

$$\log q = \log K + \bar{\mathbf{n}}\,(\log [HL]_o + \mathrm{pH}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

which was derived earlier by different reasoning by several authors (Kolthoff and Sandell, *J. Amer. Chem. Soc.*, **1941**, **63**, 1906; Irving and Williams, *J.*, 1949, 1841). The slope of the plot of $\log q$ against pH ($[HL]_o$ being constant) yields an integral value for $\bar{\mathbf{n}}$ in some cases (see, *e.g.*, Connick and McVey, *J. Amer. Chem. Soc.*, **1949**, **71**, 3182; Suttle, *ibid.*, 1954, **76**, 2184; Cornish, A.E.R.E. C/R 891; Dyrssen and Dahlberg, *Acta Chem. Scand.*, 1953, **7**, 1186); this indicates that appreciable extraction can occur in spite of a low value of $\bar{n}$ owing to a favourable combination of values of the partition coefficient and stability constants. However, in other cases non-integral values for the slope $(\bar{\mathbf{n}} - \bar{n})$ will be

found (see, *e.g.*, Irving, Bell, and Williams, *J.*, 1952, 356; Rydberg, *Acta Chem. Scand.*, 1950, **4**, 1503; *Arkiv Kemi, Min., Geol.*, 1953, **5**, 413; Dyrssen, *Svensk Kem. Tidskr.*, 1953, **65**, 43; 1954, **66**, 234).

(d) ***Extraction from strong acids.*** If HL is a strong acid and the only source of the ions H^+ and L^-, then provided $C_M \ll C_{HL}$, we have $[H^+] = [L^-] = C_{HL}$. Substituting into equation (5*a*) and differentiating, we have

$$(\partial \log q/\partial \log C_{HL})_{[M]} = \bar{\mathbf{m}}(\bar{\mathbf{h}} + \bar{\mathbf{n}}) - \bar{m}(\bar{h} + \bar{n}) = (\bar{\mathbf{h}} - \bar{h}) + (\bar{\mathbf{n}} - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad (10)$$

for mononuclear species. This is a particularly useful result since the readily measurable variations in q with the total acid concentration, C_{HL}, provide a useful check upon deductions made from the values of the partial derivatives $(\partial \log q/\partial \log [H])_{[M],[L]}$ and $(\partial \log q/\partial \log [L])_{[M],[H]}$. Thus, if ML_3 undergoes partition, values of the latter derivative and of $(\partial \log q/\partial \log C_{HL})_{[M]}$ would be $(3 - \bar{n})$ in either case. But if, *e.g.*, an acido-complex of formula HML_4 was the species in the organic phase and was almost completely dissociated into H^+ and ML_4^- in the aqueous phase, $\bar{\mathbf{h}} = 1$, $\bar{h} = 0$, and $\bar{\mathbf{n}} = 4$, so that the values of these derivatives would be $(5 - \bar{n})$ and $(4 - \bar{n})$, respectively. A decision between these two alternatives can then be made (cf. Irving and Rossotti, Part III). If, however, the acido-complex were appreciably associated in the aqueous phase, or dissociated in the organic phase, it might be impossible to distinguish unambiguously between its extraction and that of a hydrogen-free complex from considerations of partition equilibria and the valency, ν, of the metal alone. Independent determinations of $\bar{n}$, or supplementary studies of, *e.g.*, the conductivity of the organic phase might be necessary.

(e) ***Step-equilibria in the aqueous phase.*** The concentration of any non-acidic, mononuclear species, ML_n, in a system of complexes in step equilibrium in a monophase is simply related to its degree of formation, α_n, the total metal concentration, C_M, and the concentration of free ligand, [L], by the expressions

$$ML_n = \alpha_n C_M = \beta_n[L]^n / \sum_0^n \beta_n[L]^n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

If p_n is the partition coefficient of this species, and C is the total concentration of metal in the aqueous phase we have

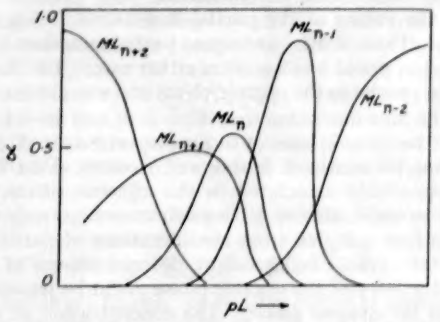
$$q = [ML_n]_o/C = p_n\alpha_n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Equations (11) and (12) emphasise the close dependence of the distribution ratio [and thence the percentage of extraction $E = 100q/(1 + q)$ for equal phase volumes] upon the values of the partition coefficient of the extracted species, the stability constants governing equilibria in the aqueous phase, and the free ligand concentration in the aqueous phase. Fig. 1 represents a typical set of curves for the degree of formation of each of a system of complexes of general formula ML_n, expressed as a function of the free ligand exponent, pL. The distribution ratio will follow α_n of equation (12) and if ML_n were the (uncharged) species extracted (cf. Fig. 1), q would pass through a maximum as the free ligand concentration is increased. But if ML_{n-2} (or ML_{n+2}) were the uncharged species extracted, Fig. 1 shows that q would steadily decrease (or increase) with [L]. The extraction of thorium or uranyl oxine complexes (Dyrssen, *locc. cit.*) and of ferric thiocyanate (Mitchell and MacDonald, *J.*, 1951, 1310) illustrates such behaviour. If the domain of ML_n were more extensive than that shown in Fig. 1, the maximum value of q would be maintained over a wide range of pL values, *e.g.*, between pL = 4 and 8 in the case of thorium and 8-hydroxyquinoline. If the species which undergoes partition is the highest complex that is formed in the system, q will not fall off from its maximum value ($\sim p_n$) with increasing free ligand concentration (cf. the case of $ThAa_4$, Rydberg, *loc. cit.*). But if the domain of ML_n is very restricted, q may never become large even when the partition coefficient, p_n, is very large. An extreme case is provided by the mercury halides. The stability constants (Sillén, *Acta Chem. Scand.*, 1949, **3**, 539) are such that if the dihalide is dissolved in water the predominant species is HgX_2. The 1 : 3 complexes, HgX_3^-, have an extremely limited

range of existence so that the addition of very small concentrations of free halide ions to a solution of the dihalide in water abruptly decreases the concentration of HgX_2 in favour of HgX_4^{2-}. Accordingly, the distribution of HgX_2 into ether decreases continuously and rapidly with increasing halogen acid concentration (Hantzsch, *Z. physikal. Chem.*, 1899, **30**, 258; Mylius and Huttner, *Ber.*, 1911, **44**, 1315).

Depending then on values of β_n and p_n for particular systems, the widest variations in behaviour can be expected. Dyrssen and Sillén (*loc. cit.*) have discussed many possible types, but in extending the treatment of the solvent extraction of metal complexes in step-equilibria from the particular case of inner complexes to the wider field of inorganic salts and acido-complexes, particular interest attaches to systems of low stability.

FIG. 1.



(f) *The partition of several species in equilibrium.* The concentration of the acido-complex, HML_{n+1}, in the organic phase is given by $p_aK_a[H^+][ML_{n+1}^-]$, where p_a is the appropriate partition coefficient, and $K_a = [HML_{n+1}]/[H^+][ML_{n+1}^-]$, so that if both uncharged ML_n and the acido-complex HML_{n+1} are extracted simultaneously

$$q = \alpha_n p_n + \alpha_{n+1} p_a K_a [H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

and it will be obvious that values of $(\partial \log q/\partial \log [L])_{[H],[M]}$ will lie between those for which α_n and $\alpha_{n+1} = 0$. Specifically the limiting value of $\partial \log q/\partial \log [L]$ as the free ligand concentration tends to zero will be $(n - \bar{n})$; and as [L] tends to infinity, $(1 + n - \bar{n})$. At intermediate values of [L], the magnitude of the derivative of equation (13) will depend on the constants of the system. Thus

$$(\partial \log q/\partial \log [L])_{[H],[M]} = (n - \bar{n}) + c[L]/(1 + c[L]) \quad . \quad . \quad . \quad (14)$$

where $c = p_aK_aK_n[H^+]/p_n$, and K_n is the equilibrium constant for the reaction $ML_{n-1} + L \rightleftharpoons ML_n$. Hence if the value of $p_aK_a[H^+] \ll p_n/K_n$, the value of equation (14) will approximate to $(n - \bar{n})$; but if $p_aK_a[H^+] \gg p_n/K_n$, it will approximate to $(1 + n - \bar{n})$.

When several species are co-extracted we can write

$$q = \sum_0^n \alpha_i p_i + \alpha_{n+1} p_a K_a [H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

Individual values of α_i can be calculated from the magnitude of [L] and the stability constants of the system, where these are known, so that, in favourable cases, individual values of p_i and p_aK_a can be calculated from a sufficient number of simultaneous equations of the form (15). This has been attempted in analysing data from experiments in which $InBr_3$ and $HInBr_4$ are co-extracted (Irving and Rossotti, Paper III). A further complication sometimes encountered, *viz.*, that alkali-metal salts or ion-pairs of the type AML_{n+1} can also be co-extracted under certain conditions (*loc. cit.*), can be treated quantitatively by an obvious extension of equation (15). Since q depends upon the product of terms α_i and p_i it will be obvious that the species which predominates in the organic phase may only contribute to a relatively insignificant extent to the total metal concentration of the aqueous phase.

(g) *The solvent extraction of salts of type* (iv). In the previous cases the ligand, L, has been a base conjugate to an acid HL. But when dealing with complexes of the type M_mL_n it is formally immaterial whether L should be regarded as the ligand attached to M, or *vice versa*. If, then, we consider, *e.g.*, the per-rhenate ion, ReO_4^- as the central group, M, and the tetraphenylarsonium ion, Ph_4As^+, as the ligand L (derived in this instance from the salt $Ph_4As^+Cl^-$), the foregoing mathematical treatment leads immediately to equations for the solvent extraction of $[Ph_4As^+][ReO_4^-]$ and similar compounds which are more general and exact than those used by Tribalat (*Analyt. Chim. Acta*, 1949, **3**, 113; 1950, **4**, 228). Considerations of electroneutrality impose the conditions $\nu = n\lambda$ as in the extraction into *o*-dichlorobenzene of, *e.g.*, $[SbI_4^-][L^-]$, $[Cu(CNS)_4^{2-}][L^+]_2$, $[Co(CNS)_4^{2-}][L^+]_2$, and $[Fe(CNS)_6^{3-}][L^+]_3$ ($L^+ = Ph_3MeAs^+$; Gibson, *Rev. Pure Appl. Chem., Roy. Austral. Chem. Inst.*, 1954, **4**, 101, and refs. therein). The equations are further simplified by the fact that only mononuclear complexes can be formed since the species, M, is already co-ordinatively fully saturated.

(h) *The solvent extraction of acids.* Polybasic acids may conveniently and logically be treated as resulting from the successive attachment of the ligand H^+ to a central anionic core X^{-h}. Equation (*5a*) may then be applied to the solvent extraction of acids of general composition H_hX_x by setting $M = X$, $m = x$, and putting $n = 0$. Thence

$$\log q = A' + \log (\bar{h}\bar{x}/\bar{h}\bar{\bar{x}}) + (\bar{h}\bar{x} - \bar{h}\bar{\bar{x}}) \log [H^+] + (\bar{x} - \bar{\bar{x}}) \log [X] \quad . \quad (15)$$

under the limiting conditions outlined above for ideal systems, *i.e.*, at low total acidities. A' is a function of stability constants and partition coefficients and may be eliminated by differentiation. For a strong monobasic acid, HL, we have $\partial \log q/\partial \log C_{HL} = (\bar{h} - \bar{\bar{h}})$, so that the gradient of the double logarithmic plot of the distribution ratio against total acid concentration can be used to determine differences between the ligand numbers of hydrogen in the two phases. If it is assumed that $\bar{\bar{h}} = 0$ at low total acid concentrations, *i.e.*, that there is complete dissociation in the aqueous phase, the degree of association of the acid in the organic phase follows immediately.

Archibald (*J. Amer. Chem. Soc.*, 1932, **54**, 3178) and Crittenden and Hixson (*Ind. Eng. Chem.*, 1954, **46**, 265) have approached a similar problem by considering plots of log $[acid]_o$ against log $[acid]_{aq.}$ from which it appears that hydrochloric and nitric acids are appreciably associated in the lower alcohols and ketones, and still more so in ethers and higher homologues of alcohols, ethers, and ketones. Measurements of the extraction of hydrochloric acid and hydrobromic acid into diethyl and di*iso*propyl ether (Chalkley and Williams, Part II) confirm that association is appreciable even at moderate acidities. By an E.M.F. method (Everett and Rasmussen, *J.*, 1954, 2812) hydrogen chloride has been shown to be a weak acid in acetone with a dissociation constant of about 10^{-8}.

A modified treatment when [M] *cannot be held constant.* When the condition $[M] \ll C_M$ is no longer valid, some progress can still be made in interpreting partition data. Using the same notation as before, we define a new function, $\bar{n}_T$, *viz.*, the overall formation function of the system (*i.e.*, the average number of ligands bound per atom of metal in the two phases considered together), by the equation

$$\bar{n}_T = \frac{\bar{m}\bar{n}\ p_{\bar{h}\bar{m}\bar{n}}\beta_{\bar{h}\bar{m}\bar{n}}[H]^{\bar{h}\bar{m}}[M]^{\bar{m}}[L]^{\bar{m}\bar{n}} + \bar{\bar{m}}\bar{\bar{n}}\beta_{\bar{\bar{h}}\bar{\bar{m}}\bar{\bar{n}}}[H]^{\bar{\bar{h}}\bar{\bar{m}}}[M]^{\bar{\bar{m}}}[L]^{\bar{\bar{m}}\bar{\bar{n}}}}{(C)_o + (C)_{aq.}} \quad . \quad . \quad (16)$$

Here the equilibrium phase volumes are assumed to be equal and the total concentration of metal in the organic phase, $(C)_o = \bar{m}\ p_{\bar{h}\bar{m}\bar{n}}\beta_{\bar{h}\bar{m}\bar{n}}[H]^{\bar{h}\bar{b}}[M]^{\bar{m}}[L]^{\bar{m}\bar{n}}$, and the total concentration of metal in the aqueous phase, $(C)_{aq.} = \bar{\bar{m}}\ \beta_{\bar{\bar{h}}\bar{\bar{m}}\bar{\bar{n}}}[H]^{\bar{\bar{h}}\bar{\bar{m}}}[M]^{\bar{\bar{m}}}[L]^{\bar{\bar{m}}\bar{\bar{n}}}$. Since $q = (C)_o/(C)_{aq.}$, equation (16) reduces to

$$(C_L - [L]_T)/C_M = \bar{n}_T = (\bar{n} + \bar{\bar{n}}q)/(1 + q) \quad . \quad . \quad . \quad . \quad . \quad (17)$$

where $[L]_T$ is the total concentration of free ligand. Differentiating, we have

$$\partial q/\partial (C_L - [L]_T) = (1 + q)^2/C_M(\bar{\bar{n}} - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad (18)$$

which can be transformed into an equivalent form

$$\partial(C_L - [L]_T)/\partial E = 100C_M(\bar{n} - \bar{\bar{n}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (17a)$$

by introducing the relation $E = 100q/(1 + q)$. By an entirely similar procedure we obtain

$$(C_H - [H]_T)/C_M = (\bar{\bar{n}} + \bar{\bar{h}}q)/(1 + q) \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

whence

$$\partial q/\partial(C_H - [H]_T) = (1 + q)^2/C_M(\bar{\bar{h}} - \bar{h}) \quad . \quad . \quad . \quad . \quad . \quad (20)$$

and

$$\partial(C_H - [H]_T)/\partial E = 100C_M(\bar{\bar{h}} - \bar{h}) \quad . \quad . \quad . \quad . \quad . \quad (20a)$$

If it is possible to measure $[L]_T$, the difference between the average ligand numbers of the complex species in the two phases can be determined from the plot of q against $(C_L - [L]_T)$ by using equation (18). That in the aqueous phase, $\bar{n}$, may be calculable from a knowledge of the relevant stability constants, so that $\bar{\bar{n}}$ may be computed. Alternatively, the ligand number in the organic phase may be known from other sources so that $\bar{n}$ may be calculated, and thence from a sufficient number of pairs of values of $\bar{n}$ and [L], the stability constants, β_n, may be obtained. A similar treatment of equation (20) leads to the differences between the ligand numbers of hydrogen in the two phases which can be further discussed on the lines outlined above.

Summarising Discussion of Ideal Systems.—The extraction of undissociated compounds of type (i) is readily described in terms of the Nernst partition isotherm and needs no elaboration here (cf. Friedman, *locc. cit.*). There are, however, a number of interrelated reasons for the apparent differences between the behaviour of inner complexes of type (ii) and inorganic salts of type (iii).

When the acid HL is weak, and the complex ML_n is strong and unsolvated [as is usually the case with type (ii) solutes], the primary stage in extraction—considered in terms of equilibrium rather than mechanistically—is the formation of this complex from constituent ions at such a low free-ligand concentration that the solvent characteristics of the aqueous phase are not appreciably modified. The inner complexes are stable, stoicheiometric, monomeric compounds which can usually be isolated in the solid state. They are very sparingly soluble in water, but are usually extracted readily into chloroform, carbon tetrachloride, benzene, and hexone (*iso*butyl methyl ketone), but poorly into ethers and alcohols. The organic reagent, HL, from which they are derived is a comparatively weak acid and more soluble in organic solvents than in water. Changes in the solvent, and extensive variations in the composition of the aqueous phase due to the addition of other ions, do not affect the composition of the extracted species. The extraction of an (unsolvated) inner complex does not introduce water into the organic phase, and changes in the mutual solubility of the two phases are very small even when the free ligand concentration is varied sufficiently to change the extractability over a wide range of distribution ratios. Since changes in the mutual solubility of the phases are negligible, the constancy of (stoicheiometric) partition coefficients and stability constants may be assumed if the ionic strength of the aqueous phase is held constant. Such systems may usually be described quantitatively by equations of the form (*5a*) and it is possible to compute from experimental data the partition coefficient of the single extracted species and also one or more of the stability constants which refer, it should be noted, to an aqueous solution saturated with organic solvent. If the extraction of an inner complex into a number of solvents is " ideal " in each case, then plots of log q against pL will be parallel for the different solvents. This will no longer be the case if the complex is solvated to different extents by the various organic solvents, for the simplification of equation (*5*) to (*5a*) will no longer be valid.

Weak complexes are involved in the extraction of complexes of type (ii), so that a much higher ratio of ligand to metal concentration is required. The species extracted can rarely be isolated, and often even its composition is in doubt: there is reason to suppose that it varies in many cases with the experimental conditions. Extraction is highest into ketones, ethers, alcohols, and similar donor solvents, but is generally negligible into chloroform or hydrocarbons. The acid from which the anion of the salt is derived is strong and usually

undergoes partition appreciably into the organic phase only at the highest concentrations. When changes in the concentration of anion are brought about by changing the concentration of the corresponding mineral acid (and this is usually the case) there may be gross changes in the volumes of the two phases, their direction and magnitude depending specifically on the organic solvent and acid employed. Hence under the conditions of experimentation, both the partitition coefficients and the stability constants are variables which change with phase composition, so that most systems deviate more or less from the behaviour predictable for ideal systems. However, by selecting mineral acid and organic solvent such that changes in mutual solubility are negligible over a sufficiently wide range of values of q, it appears that the extraction of salts of type (iii) (*e.g.*, the extraction of indium bromide from hydrobromic acid into *iso*butyl methyl ketone; Irving and Rossotti, Parts III and IV) can be treated on the lines developed for ideal systems.

It is impossible, at present, to control the ionic strength of an organic phase in solvent extraction, for although lithium perchlorate can be used for controlling the ionic strength of an anhydrous ethereal solution (Berglund and Sillén, *Acta Chem. Scand.*, 1948, **2**, 116) this expedient cannot be employed in a two-phase system. But when formally uncharged inner complexes are extracted and at low concentration, we shall expect comparatively small changes in their activity coefficients over the range of experimental conditions, though such cannot be the case when inorganic salts and acido-complexes are extracted. This provides another reason why the extraction of inner complexes should be easier to interpret quantitatively than that of type (iii).

The addition of neutral salts to the aqueous phase in attempts to control the ionic strength may either increase or decrease the extraction of inorganic salts in highly specific ways (Jenkins and McKay, *Trans. Faraday Soc.*, 1954, **50**, 107; Bock and Bock, *Z. anorg. Chem.*, 1950, **263**, 146) and it is noteworthy that, although the distribution generally remains substantially independent of metal concentration when inner complexes are extracted, yet it may remain constant, increase, or decrease with increasing metal concentration where inorganic salts of type (iii) are concerned. The solvent extraction of salts of type (iv) shows features of type (ii) in the main, though few systems have been examined quantitatively in any detail.

Solvent Extraction in Non-ideal Systems.—Glueckauf, McKay, and Mathieson (*Trans. Faraday Soc.*, 1951, **47**, 437) have indicated the lines on which the Gibbs–Duhem equation can be applied to the study of partition in what we have termed non-ideal systems. However, qualitative information about possible variations in behaviour in such systems can be obtained more readily by considering selected phase-diagrams.

If V_o', V' are volumes of an organic solvent and an aqueous solution, and V_o, V the corresponding volumes after equilibration, we have in practice the result that $V_o \neq V_o'$, and $V \neq V'$. The extent of mutual miscibility is determined by the nature of the organic solvent, the initial composition of the aqueous phase, the extent to which different species present are distributed between the two phases, and the actual composition of these solutes. If, in dealing with the extraction of an inorganic salt from hydrochloric acid the restriction $C_M \ll C_{HCl}$ is applied (*e.g.*, by using tracer or microgram quantities of metal) the behaviour of the system as a whole will not differ significantly from that of the simpler two-phase condensed system of three components, *viz.*, water–organic solvent–hydrogen chloride. Since the behaviour of this basic system—at least so far as changes in phase ratio and solvent composition are concerned—will serve as a common pattern for the extraction of any metal chloride, outstanding differences must be interpreted as due to specific properties, *e.g.*, stabilities or partition coefficients of the metal–chloride ion–proton system already discussed under the heading of ideal systems.

Consider the isotherm for the system diethyl ether–water–hydrogen chloride which is illustrated (not to scale) in Fig. 2. After equilibration, a mixture of equal volumes of water and ether of composition represented by the point C will separate into an ether-rich phase A and a water-rich phase B. The partition coefficient of any solute will depend on the solvent properties of the two phases and is given approximately by the ratio of its solubility in them. On addition of hydrogen chloride to a mixture of composition C (or on equilibrating equal volumes of ether and hydrochloric acid), the total composition moves

along the line $CC'C''H$. The volume of the ether phase decreases relative to that of the aqueous phase (cf. Fig. 3) and becomes zero at H, the boundary of the binodal curve AHB. For all mixtures of ether and hydrochloric acid with total compositions corresponding to points along a tie-line (*e.g.*, $A'C'B'$) the relative volumes of the two phases will vary according to the position of C', but their compositions are determined solely by the positions of the points A' and B'. Hence, the partition coefficient for each solute species which is distributed between the phases will be constant for all ether–hydrochloric acid compositions represented by points along the line $A'B'$; the same will be true for the stability constants in each phase for all species in equilibrium. Hence, values of q will be constant along any one tie-line, irrespective of the number of species partitioned (cf. equations 13 and 15). On the other hand, since the percentage extracted is given by

$$E = \frac{100C_oV_o}{(CV + C_oV_o)} = \frac{100qR}{(1 + qR)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

where $R = V_o/V$ is the ratio of the phase volumes after equilibration, the percentage of extraction will vary along a tie-line according to the position of C', decreasing as C'

FIG. 2. *The phase isotherm for water–ether–hydrogen chloride.* (Not to scale.)

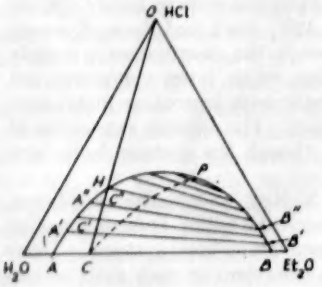
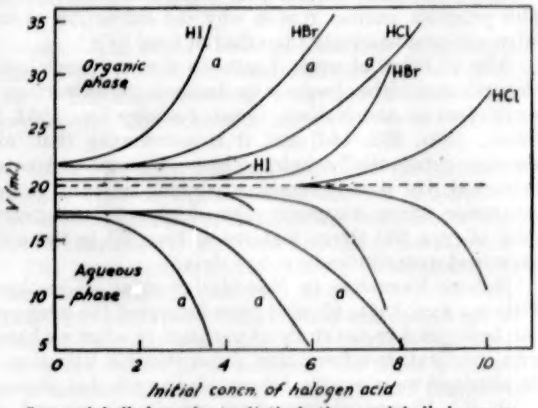


FIG. 3. *Volume changes on equilibration of 20 ml. of an ether with 20 ml. of halogen acid.*



Curves labelled *a* refer to diethyl ether, unlabelled curves to di*iso*propyl ether, and the broken line to 2 : 2′-dichloroethyl ether.

approaches A'. Since for successive mixtures of composition C, C', C'', ... the composition of the organic phases A, A', A'', . . . and that of the corresponding aqueous phase B, B', B'', ... becomes progressively more alike, the partition coefficient will decrease as the point of complete miscibility, H, is approached : but it may retain a value $\gg 1$ even at this point. A common practice in studying extraction is to equilibrate equal volumes of organic solvent and aqueous phases of different composition. Only a limited range of phase compositions (and partition coefficients) can be explored by following such a path as $CC'C''H$, since complete miscibility is reached at the point H where the phase compositions at the extremes of the tie-line may still be very dissimilar. A fuller study would be achieved by choosing compositions along a line joining the plait-point, P, to a point on the base line such that the phase ratios after equilibration are always the same. The organic and the aqueous phase become indistinguishable at the point P, so that for two phases coexisting at a point immediately within the heterogeneous region, the partition coefficient, p, is equal to unity for all species, and equilibrium constants for any given process will be identical in the two phases.

As P is approached, the increasing similarity of phase composition will make the physical separation of phases more and more difficult. Though this presents an increasingly

serious practical disadvantage in batch or counter-current extraction, the objection is of little weight in partition chromatography (Irving and Williams, *Sci. Progress*, **1953**, **41**, 418).

If the plait-point lay on the other side of *H*, equilibration of mixtures of composition lying along *CC'C''H* would give organic phases increasing in volume and water content, while the aqueous phases would be less modified by increasing acidity. Such a system is found with *iso*pentyl alcohol–water–hydrochloric acid. Volume changes which occur in a large number of other systems are reported elsewhere (Irving and Rossotti, Part V), and Fig. 3 shows some typical results for the volume changes which occur on equilibrating initially equal volumes of halogen acids and three different ethers. The decrease in the volume of the organic phase at the expense of the aqueous phase is more pronounced when hydrochloric acid is replaced by hydrobromic acid, and complete miscibility is reached at a lower acidity: similar effects are observed when hydrobromic acid is replaced by hydriodic acid. These changes are not due to the greater partition of hydrobromic (or hydriodic) acid as compared with hydrochloric acid, and there is no striking difference in the concentration of water in the organic layer. For any one acid the effects become less pronounced in ascending a homologous series of organic solvents. With *iso*pentyl alcohol, however, the volume of the organic phase increases at the expense of the aqueous phase, the effects increasing in the order HBr < HCl < HI. The partial inversion of order possibly reflects anomalies in the solvation of the halogen acids similar to those noted for the solvation of uranyl nitrate (McKay, *Trans. Faraday Soc.*, 1952, **48**, 1103) and cobalt chloride (Katzin and Ferraro, *J. Amer. Chem. Soc.*, 1953, **75**, 3821) in the presence of alcohols. At high acidities the behaviour of *iso*pentyl acetate is similar because the formation of the parent alcohol becomes appreciable even during the short period required for the equilibration. In contrast to the effects of halogen acids, the equilibration of diethyl ether with nitric acid leads to increases in the volume of the organic phase relative to the aqueous phase.

The Extraction of Metal Salts under Non-ideal Conditions.—Information of the above nature derived from studies of the equilibration of an organic solvent and mineral acids of different concentrations should be immediately applicable to the partition of metallic salts in such mixtures, provided the total concentration of metal is sufficiently low as not to modify the phase isotherms. But since there is abundant evidence that metal acido-complexes are hydrated in the organic phase, the extraction of macro-concentrations of an inorganic salt in this form will entail the transport of appreciable quantities of water into the organic phase, so that a full investigation would demand the investigation of a four-component system. Some progress can be made by comparing the concentration of water in the organic phase, measured after equilibration with an extractable salt, with that which obtains when the salt is omitted from the aqueous phase or, better, replaced by an equivalent concentration of a non-extractable salt of similar type (cf. Katzin and Sullivan, *J. Phys. Colloid Chem.*, 1951, **55**, 346; Yates, Laran, Williams, and Moore, *J. Amer. Chem. Soc.*, 1953, **75**, 2212). In the absence of extractable metallic salt we find the concentration of water in diethyl ether to be about twice as high as in *iso*propyl ether equilibrated at the same acid concentration. For both solvents the concentration of water decreases with initial acidity and passes through a flat minimum at $N' \sim 5$M (cf. Campbell, Laurenne, and Clarke, *ibid.*, 1952, **74**, 6193). Despite individual differences of this nature we have observed certain regularities even in cases of non-ideal extraction which are described below.

Maxima in Curves of Percentage Extraction: Retrograde Extraction.—Consider the extraction of iron from hydrochloric acid into ether in the form of $FeCl_3$ or $HFeCl_4$ (Part II). The distribution ratio, q, depends on the product of a partition coefficient, p_i, and the degree of formation, α_i, of the corresponding partitionable species (cf. equation 13). For phase compositions represented by a tie-line on or near the base line of Fig. 2, p may be large and favourable to extraction. However, at low acidities (and hence low free ligand concentrations) the degree of formation of $FeCl_3$ and $HFeCl_4$ is so low that the distribution ratio, q, is very small. In 4—5M-hydrochloric acid, the degree of formation of the complex species has increased considerably (Gamlen and Jordan, *J.*, 1953, 1435) and q has

become large enough for the percentage of extraction to be quite high. Up to this stage changes in phase miscibility due to the presence of acid are comparatively small and the treatment corresponds approximately to that of ideal extraction already discussed. Now increase of the acidity still further to 7M or above certainly ought to increase the degree of formation of $FeCl_3$ and $HFeCl_4$ still further, for there is no evidence of the formation of higher complexes. But if the increased miscibility produces concomitant decreases in the partition coefficient of the extracted species, q may pass through a maximum.

If q passes through a maximum, there will normally be a maximum in the value of E, the percentage of extraction [cf. equation (21)]. But the falling-off in extraction after a maximum has been reached—" retrograde extraction " as it may be termed—may be due to a combination of effects whose relative importance will vary from system to system. In " ideal " systems in which the phase ratio, R, of equation (21) and all stability constants and partition coefficients are effectively constant, a maximum in q (and in E) is adequately explained by considerations of sequential equilibria (p. 1911) if the degree of formation α_i of the extracted species passes through a maximum with increase in free ligand concentration. While this may still be one of the factors operating in non-ideal systems the added feature here is the possibility of decreases in partition coefficients due to changes in phase composition. It follows from equation (13*a*) that the sign and magnitude of the derivative $\partial q/\partial \mathrm{pL}$ will depend on those of the partial derivatives $\partial \alpha_i/\partial \mathrm{pL}$ and $\partial p_i/\partial \mathrm{pL}$. Where, in the absence of changes in solvent character, α_i would pass through a maximum, concomitant decreases in p_i will bring about retrograde extraction at still lower values of pL. But where α_i is a monotonic increasing function of pL, retrograde extraction is still possible provided concomitant decreases in p_i are large enough. When such is the case, the onset of retrograde extraction may well be primarily a function of solvent composition and largely independent of the substances extracted. Thus for the chlorides of Fe^{3+}, Ga^{3+}, and Tl^{3+}, maximum extraction into ether occurs from hydrochloric acid of concentration ~7M, while for the bromides of Ga^{3+}, In^{3+}, Tl^{3+}, Fe^{3+}, and Tl^{+} the acid concentration is about 4·5M, and for iodides of Tl^{+}, Tl^{3+}, and In^{3+} it is about 2M (Irving and Rossotti, *Analyst*, 1952, **77**, 801).

Changes in phase ratio must be taken into account in considering percentage extraction [cf. equation (21)]. In " ideal " systems these are negligible. In " non-ideal " systems they may increase more or less rapidly (cf. Fig. 3) with changes in initial acidity and will tend to exaggerate the maximum in the curve of percentage extraction against acidity (or ligand concentration). But in some systems, *e.g.*, extraction from nitric acid into ether, R actually increases with acid concentration; q does not pass through a maximum and retrograde extraction is not normally observed over the range of acid concentrations accessible to experiment.

Extraction by Different Solvents.—Where it is possible to use the approximate expression

$$p = \frac{\text{solubility of a species in the organic solvent}}{\text{solubility of the same species in water}} = S_o/S$$

the relation $\log p = (\log S_o + \text{constant})$ should hold for a number of organic solvents. This has been confirmed for the partition of the weak monobasic acid dithizone between water and a wide range of organic solvents decreasing in efficiency in the order chloroform, *o*-dichlorobenzene, chlorobenzene, benzene, toluene, carbon tetrachloride, *cyclo*hexane, and *n*-hexane (Irving and Tilley, unpublished work). Discrepancies occur when solvents of greater miscibility with water are employed. Substantially the same order might be expected for inner complexes. But where both water and organic solvent are capable of strong intermolecular attraction with each other and with dissolved species, as will be the case when the extraction of inorganic complexes into donor molecules such as ketones, alcohols, and ethers is under consideration, no such order may hold. For predominantly covalent inorganic complexes which can be expected to have a low polarity, *e.g.*, HgI_2, intermediate behaviour would be expected. It seems unlikely, therefore, that any generally applicable " order of solvent efficiency " could be given.

One great practical difficulty in attempting to draw up such an order may be illustrated

by the observations that iron is extracted more completely by diethyl ether than by di*iso*propyl ether from 4M-hydrochloric acid, but that the order of efficiency is reversed with 9M-acid. On the other hand, it would be of great value to the analyst if some sort of prediction could be made. It has frequently been observed that the lower members of a homologous series extract inorganic complexes more effectively than higher members, and it appears to be a rough guide that the more miscible the phases in the absence of acid, the more effective the extraction. This is consistent with the order ethyl methyl ketone > methyl *iso*propyl ketone > ethyl acetate > ethyl ether > . . . . . benzene, often noted. For the extraction of similar substances, *e.g.*, indium as the acido-complex $HInX_4$,aq., from hydrochloric, hydrobromic, and hydriodic acids, the order methyl propyl ketone > methyl *iso*propyl ketone > *iso*butyl methyl ketone > furfuraldehyde > ethyl acetate > diethyl ether > *iso*pentyl alcohol > *iso*pentyl acetate > 2 : 2′-dichlorodiethyl ether > di-*iso*propyl ether > hydrocarbons is generally valid. Much the same order holds for the extraction of other acido-complexes, *e.g.*, of gold, gallium, or iron, from halogen acids, and for a number of nitrates from nitric acid (Part V, and refs. therein).

Discrete changes in partition coefficient are effected when one solvent is replaced by another. The behaviour of mixtures of solvents has not been widely studied although many empirical observations have been recorded. Changes in the partition of hydrochloric acid, of water, and of ferric chloride brought about by adding methanol progressively to ether–hydrochloric acid mixtures are reported elsewhere (Chalkley and Williams, Part II). The percentage of indium extracted from hydrobromic acid by a mixture of two solvents is found to agree with that calculated from the mixture law in certain cases (Irving and Rossotti, unpublished work), but in the extraction of rare-earth nitrates from tributyl phosphate mixtures no such simple treatment is adequate (Peppard, Faris, Gray, and Mason, *J. Phys. Chem.*, 1953, **57**, 294).

The Order of Extractability of Different Metals.—A series of tris-complexes of, *e.g.*, 8-hydroxyquinoline and tervalent metals should be strikingly alike and consist of a comparatively large organic matrix with an inner core of metal occupying a comparatively small fraction of the total molecular volume and completely shielded from the solvent. Solvation by water or organic solvent may well be small and should at least be constant from one metal complex to the next. There should not, therefore, be significant differences in their partition coefficients, and differences in extractability ought to be determined primarily by considerations of sequential equilibria; any order of increasing extractability for different metals ought thus to be independent of the extracting solvent used. When, however, the extent of solvation by water and organic solvent changes from one metal complex to another, the order of extraction will depend more or less specifically on the solvents and complexes concerned. Since any change in acidity in the aqueous phase modifies the relative activity of these two solvents, the relative extractability of two metals into a given solvent may become a function of acidity even when considerations of hydrolysis can be dismissed (cf. Peppard *et al.*, *loc. cit.*). Several of the more general points raised in this paper will be discussed in the following Parts II—V in relation to specific systems.

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THE INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

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*The Extraction of Ferric Chloride into Non-aqueous Solvents.**

By D. E. Chalkley and R. J. P. Williams.

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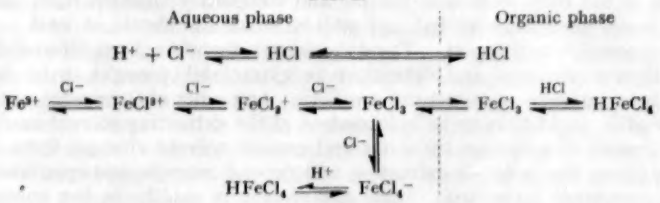
The distributions of hydrochloric and hydrobromic acids between water and diethyl and di*iso*propyl ethers have been studied. Both phases have been analysed for acid, and the ether phase for water content. The distribution of ferric ions in the hydrochloric acid–ether–water systems has also been re-examined. The addition of methanol to the two-component, two-phase system of ethyl ether and aqueous hydrochloric acid affects the distribution of hydrochloric acid and ferric ions in a relatable fashion. Suggestions are made about the mechanism of these and similar extractions.

On the addition of hydrochloric acid to an aqueous ferric salt solution the amounts of the various possible ferric chloride complexes formed depend upon the final concentrations of the ions in solution in accordance with recently determined equilibrium constants (Gamlen and Jordan, *J.*, **1953**, 1435). Over a limited range of acid concentration a complex, $FeCl_4H,wH_2O$, where w may well be as large as 10, can be extracted into ethers from the aqueous phase (Nachtrieb and Conway, *J. Amer. Chem. Soc.*, **1948**, **70**, 3547, 3552; Myers, Metzler, and Swift, *ibid.*, **1950**, **72**, 3767; Friedman, *ibid.*, **1952**, **74**, 5). The simplest consideration of such an extraction must include the equilibria represented in Fig. 1. Similar equilibria will be set up for other metal halides which are extractable into ethers, *e.g.*, $InBr_3$ (Part III). The derivation of equations which should describe all such extractions has been given (Part I). In this paper experimental evidence on the extraction of ferric chloride into several non-aqueous solvents will be discussed. In the first instance, however, the extraction of the simple halogen acid must be described.

Fig. 1.



Extraction of Halogen Acids by Ethyl and iso*Propyl Ethers.*—From solutions of high molarity, >3M, hydrochloric and hydrobromic acids are extracted into the two ethers in amounts determinable by direct titration. Below this molarity, indirect methods of determination must be used. We have employed simple conductivity determinations in water of the organic-phase acid recovered by a back-extraction from the ether (p. 1926). Table 1 gives the results of the measurements for the extraction of the two acids into the two ethers when equal *initial* phase volumes are used. On the whole, our findings agree with the scattered data in the literature (Bock, Kusche, and Bock, *Z. analyt. Chem.*, **1953**, **138**, 167). Although the phase changes on mixing are approximately constant over the range of acidities studied, there is always an increase in volume of about 5% in the aqueous phase.

In Part I it was shown that the distribution coefficient, q, of an acid should be given by

$$\partial \log q/\partial \log C_{HL} = \bar{\mathbf{h}} - \bar{h} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where C_{HL} is the total acid in the system and $\bar{\mathbf{h}}$ and $\bar{h}$ are the average number of hydrogens bound per ligand atom, L, in the organic and the aqueous phase respectively. This

* This is Part II of a group of papers of which Part I is the preceding paper and Parts III, IV, and V are the following papers.

equation assumes that activities are constant, which is not true here. Now, from Table 1, virtually all the acid remains in the aqueous phase, so that C_{HL} is given by the concentration of the aqueous acid. Equation (1) can therefore be written

$$\partial \log q/\partial \log a_{HCl} = \bar{\mathbf{h}} - \bar{h}$$

where a_{HCl} is the activity of the aqueous acid.

TABLE 1. *Distribution of hydrochloric and hydrobromic acids between water and ethyl and iso*propyl ethers. [M = Molarity of aqueous acid initially.]

(A) Ethyl ether–water–hydrochloric acid; equal initial phase volumes.

M	1·72	1·95	2·16	2·40	2·60	2·82	3·04	4·88	5·17
log a_{HCl}	0·21	0·29	0·36	0·43	0·50	0·56	0·61	1·06	—
$-\log [HCl]_{ether}$	3·70	3·60	3·55	3·50	3·40	3·28	3·25	2·80	2·65

(B) *iso*Propyl ether–water–hydrochloric acid; equal initial phase volumes.

M	2·16	2·60	2·82	3·24	3·47	4·36	4·88	5·42	6·00	8·00	10·00
log a_{HCl}	0·36	0·50	0·56	0·67	0·72	0·93	1·06	1·18	—	—	—
$-\log [HCl]_{ether}$	4·00	3·85	3·67	3·60	3·40	3·04	2·66	2·40	2·10	1·70	1·00

(C) Ethyl ether–water–hydrobromic acid and (D) *iso*propyl ether–water–hydrobromic acid; equal initial phase volumes.

	(C)							(D)						
M	1·38	1·73	2·07	2·41	2·75	3·15	3·70	2·80	3·16	3·45	3·70	4·30	5·00	5·65
$-\log [HBr]_{ether}$	4·00	3·80	3·58	3·40	3·28	3·17	2·91	4·00	3·92	3·82	3·70	3·45	3·30	3·20

Up to ~2·8M-acid, $\bar{\mathbf{h}} - \bar{h} = 0$ in both diethyl and di*iso*propyl ether extractions of hydrochloric acid, suggesting that hydrochloric acid is completely ionised in the ethers. No discussion of the extractions of hydrobromic acid can be made because of lack of activity data. In the extraction of hydrochloric acid the exponent $\bar{\mathbf{h}} - \bar{h}$ increases rapidly as the aqueous acidity increases above 3M. The results in other solvents (Part I) lead to the same observations. It should be noted that $\bar{\mathbf{h}} - \bar{h}$ may increase through changes in either the composition of the extracted species, " ideal " systems, or the partition coefficients, " non-ideal " systems. It is impossible to obtain satisfactory measurements on the extraction of hydriodic acid as it decomposes.

Variation of Water in the Organic Layer with Aqueous Acidity.—The equilibrium concentration of water extracted into *iso*propyl ether from aqueous hydrochloric acid has been shown to go through a minimum with increasing acid concentration (Campbell, Laurene, and Clark, *J. Amer. Chem. Soc.*, 1952, **74**, 6193). We have determined the concentration of water in ethyl ether equilibrated with an aqueous hydrochloric acid phase of different acid concentrations (see p. 1926) and the results are recorded in Table 2. Comparison between the results for the two ethers shows that the water in the ether layer varies in a parallel manner. However, the concentration of water in diethyl ether is always more than twice that in the *iso*propyl ether at the same acid concentration in the aqueous layer. Together with the phase volume changes this information shows that the respective ether layers

TABLE 2. *Extraction of water from aqueous hydrochloric acid into ethyl and iso*propyl ethers. (M = initial aqueous acid molarity.)

(A) Ethyl ether–water–hydrochloric acid: 5 ml. of aqueous solution shaken with 25 ml. of ether.

M	0·0	2·9	4·3	8·6	9·75	11·0	11·5
$[H_2O]_{ether}$	0·45	0·35	0·29	0·21	0·20	0·21	0·22

contain less water, whilst the aqueous phases in equilibrium with them contain more and more ether as the total acidity is increased. It is not to be expected therefore that the paritition coefficients of the acids, or their dissociation constants, will remain constant except at low acidities. Thus the distribution of metals in the systems must also be expected to be one of a " non-ideal " rather than of an " ideal " kind (cf. Part I). The distribution of acid and water is of importance in making this differentiation.

Effect of Methyl Alcohol on the Partition of Acid.—The extraction of metal halides can be

brought about by a wide variety of solvents which are only partially miscible with water. In general, it is observed that the more polar the organic solvent the more readily it extracts the halide (Part I). As an investigation of the effect of a number of different single solvents was being made (Part V), it was decided to adjust the extracting power of one solvent, ethyl ether, by adding different amounts of a third component, methanol. Such three-component solvent systems are often employed in inorganic chromatography, especially on cellulose supports. We have discussed such matters elsewhere (Chalkley and Williams, *J.*, 1954, 1718).

First, the changes in distribution of both water and hydrochloric acid between the two phases were examined over a wide acidity range. Table 3 illustrates the differences in

TABLE 3.

	M	0·0	1·1	2·2	4·2	7·8	9·6	11·5
A	Volume of lighter phase	25·0	24·8	24·4	23·7	20·7	18·0	15·4
	Volume of heavier phase	5·0	5·2	5·7	6·6	10·0	12·7	14·6
B	Volume of lighter phase	30·1	24·5	21·4	19·4	17·2	—	15·7
	Volume of heavier phase	6·1	12·1	14·9	17·0	19·6	—	21·6

final phase volumes at different acidities for the initial solvent systems: (A) 25 ml. of ether and 5 ml. of aqueous acid; (B) as (A) but with addition of 7·5 ml. of methanol. The data show that the phase volume changes on mixing are much larger in the system containing methanol if conditions of equal acidity are compared. Increasing miscibility of the phase will generally lead to departures from "ideal" behaviour at lower acidities and be accompanied by large volume changes. Measurements of the equilibrium water content of the lighter phase are given (Table 4) for the solvent system including methanol, system (B).

TABLE 4.

Initial [HCl] molarity ...	0·0	0·1	0·6	1·15	2·15	2·88	4·30	8·63	11·5
Final [H_2O] molarity...	8·9	7·4	3·9	3·3	2·5	1·9	1·3	0·3	0·23

These results can be compared directly with those given in Table 3. It seems likely that the loss of water from the lighter phases is due to the solvation of the increasing amount of acid in the aqueous phase.

We have also studied the changes in acid normality in both the aqueous and the organic phase at equilibrium as the amounts of acid and the amounts of methanol in the phases have been separately varied. In every case the final acid normality in the aqueous phase increases almost linearly with increasing total acid but the final molarity in the lighter phase undergoes much more irregular changes (Fig. 2 and Table 5). The appearance

TABLE 5. *Distribution of hydrochloric acid between the two phases formed from different mixtures of methanol, ethyl ether, and water* (Fig. 2).

In each system 25 ml. of ether, 5·0 ml. of water, and *V* ml. of methanol were taken. The initial acid concentration (M) is that in the water added; N_o and *N* give the final acid normalities in the organic and aqueous layers, respectively.

V =	0·0		5·5		7·5		8·0	
M	N_o	*N*	N_o	*N*	N_o	*N*	N_o	*N*
1·12	0·0	1·11	0·004	0·72	0·031	0·38	—	—
1·84	—	—	—	—	—	—	0·084	0·50
2·20	0·0	1·96	0·007	1·05	0·045	0·69	—	—
2·46	—	—	—	—	—	—	0·090	0·57
4·25	0·001	3·65	0·010	1·73	0·042	1·33	—	—
5·56	—	—	—	—	—	—	0·042	1·40
6·12	0·006	4·40	0·010	2·31	—	—	—	—
7·90	0·015	4·45	—	—	0·022	—	0·033	2·05
11·45	0·085	4·75	0·025	3·78	0·032	3·25	0·033	3·05

of maxima in the acid concentration in the organic phase must be a consequence of the falling water and methanol concentration in this layer which undergoes large changes in composition. In order to show how the final water and acid concentrations in the lighter

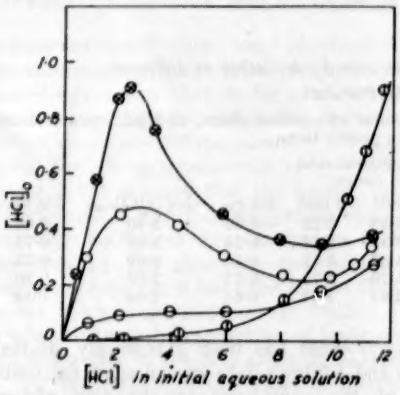
phase were related, when different amounts of methanol were added, we measured the water content of the light phases resulting from the equilibration of 25 ml. of ether, 5·0 ml. of aqueous hydrochloric acid (2·78M), and different volumes V of methanol. The results are recorded in Table 6. The two concentrations are seen to be closely related.

TABLE 6.

V, ml.	0	2·5	5·0	6·5	7·5	7·7	8·0
Final [HCl] in light phase	0·0	0·003	0·008	0·025	0·043	0·06	0·07
Final [H_2O] in light phase	0·35	0·60	1·00	1·37	2·20	3·41	4·34

Extraction of Ferric Chloride into Diethyl and Diisopropyl Ether.—In Fig. 1 a set of equilibria has been given which, as stated, should be suitable for a description of ferric chloride extractions. In the Figure there are no equilibria relating to the formation of

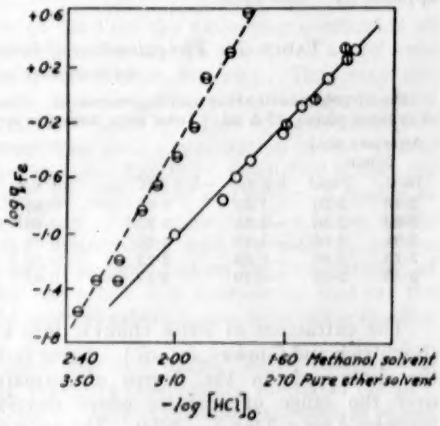
FIG. 2. *The distribution of hydrochloric acid between aqueous and organic layers, using the initial solvent systems shown.*



5 ml. of aqueous acid plus ⓘ 25 ml. of ethyl ether; ⊖ 25 ml. of ethyl ether + 5 ml. of methanol; ○ 25 ml. of ethyl ether + 7·5 ml. of methanol; ⊗ 25 ml. of ethyl ether + 8 ml. of methanol.

The intersection of the curves is a result of plotting the equilibrium organic acid concentration against the initial aqueous acid concentration and would disappear if the equilibrium acid concentration in the heavier phase were plotted for the latter.

FIG. 3. *The variation of extraction of iron (ferric), log q_{Fe}, with concentration of hydrochloric acid in the organic layer, $-\log [HCl]_o$, in the solvent systems shown.*



⊖ 25 ml. of aqueous acid, 25 ml. of ethyl ether; ⓘ○ 5 ml. of aqueous acid, 25 ml. of ethyl ether, 7·5 ml. of methanol.

The points marked ○ represent increasing acid and iron extraction with increasing total acidity and those marked ⓘ decreasing acid and iron extraction with increasing total acidity.

polynuclear complexes (cf. Part IV, and Herber, Bennett, Bentz, Bogar, Dietz, Golden, and Irvine, Abs. 126th Meeting, Amer. Chem. Soc., 1954, p. 33R). We dismissed the necessity for considering such species for the following reasons. (*a*) The spectra of ferric chloride in ether extracts from aqueous hydrochloric acid, in ethanol solutions in the presence of lithium chloride, in methanol in the presence of hydrochloric acid, in water in concentrated hydrochloric acid, and in solid compounds of formula M^IFeCl_4, where M^I is an alkali-metal cation, are all identical (Friedman, *loc. cit.*). (*b*) Analyses of ether extracts of ferric chloride from aqueous hydrochloric acid give the formula $HFeCl_4$ (p. 1920). (*c*) A Beer's law plot of the absorption of the extracts in the ether solvents is linear over the range from 10^{-3} to 1·0M. (*d*) The extraction of ferric chloride into *iso*propyl ether is independent of iron concentration over the range 10^{-5} to $10^{-2\cdot5}$M-iron at low acidities. At high acidities the extraction conditions are suspected of being "non-ideal" (p. 1921), so that large deviations are to be expected from causes other than polymerisation. In this paper

therefore it will be assumed that polymerisation is absent at low iron concentrations and acidities.

The results we have obtained on the extraction of ferric chloride into diethyl ether are given in Table 7. The total iron concentration used was $\ll 10^{-3}$M. This extraction being considered to be " ideal " the following equation holds (Part I) :

$$\partial \log q/\partial \log C_{HL} = (\bar{h} - \bar{h}) + (\bar{n} - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where q is the distribution coefficient of iron, and $\bar{h}$, $\bar{h}$, $\bar{n}$, and $\bar{n}$ refer to the degree of formation of the complexes in the two phases, the complexes in the water phase being assumed to be represented by $H_{\bar{h}}FeCl_{\bar{n}}$ and in the organic phase by $H_{\bar{h}}FeCl_{\bar{n}}$. Gamlen and Jordan (*loc. cit.*) have shown that in 2·0M-hydrochloric acid $\bar{n}$ ~2·5, and in 5·0M-acid $\bar{n}$ ~3·0. Assuming that $\bar{h}$ ~0 and knowing the formula of the extracted complex to be $H_{1\cdot0}FeCl_{4\cdot0}$, we can reduce equation (2) to $\partial \log q/\partial \log C_{HL} = 2{\cdot}5 \longleftrightarrow 2{\cdot}0$. Now as total acid is equal to the acid in the aqueous layer to a first approximation this equation can be expressed as $2{\cdot}0 \longleftrightarrow 2{\cdot}5 = \partial \log q/\partial \log a_{HCl}$ where a_{HCl} is the activity of the acid in the aqueous phase. The results show that the slope is much greater than this figure and the system is apparently " non-ideal."

TABLE 7. *The extraction of ferric ions into diethyl ether at different hydrochloric acid normalities.*

Equal volumes of ether and aqueous acid. Final volume of aqueous phase, 22·3 ml.; final volume of organic phase, 27·5 ml. Total iron, added in aqueous phase, 10^{-3}M.

Aqueous acid concn.					Aqueous acid concn.				
Initl.	Final	$\log q_{Fe}$	$-\log [HCl]_{ether}$	$\log a_{HCl}$	Initl.	Final	$\log q_{Fe}$	$-\log [HCl]_{ether}$	$\log a_{HCl}$
2·46	2·20	−1·60	3·44	0·40	3·58	3·22	−0·50	3·10	0·66
2·69	2·50	−1·38	3·37	0·46	3·81	3·41	−0·24	3·04	0·71
2·91	2·66	−1·19	3·30	0·52	4·03	3·59	0·10	2·99	0·75
3·13	2·86	−0·86	3·23	0·56	4·26	3·74	0·27	2·92	0·80
3·36	3·06	−0·70	3·17	0·62	4·47	3·93	0·64	2·85	0·84

The extraction of ferric chloride into *iso*propyl ether has been extensively studied (Nachtrieb and Conway, *loc. cit.*). Using Gamlen and Jordan's data we can again calculate the differences in the degree of formation of the complexes in the two phases over the range of acidities where distribution can be studied. Equation (3) then becomes $\partial \log q/\partial \log a_{HCl} \approx 2{\cdot}0$. The experimental results again give a much higher value of this function (Table 8). It appears safe to conclude that the sequential equilibria

TABLE 8.

Initial acid concn.	3·0	4·0	4·5	5·0	6·0
$\log a_{HCl}$	0·58	0·85	0·97	1·08	1·29
$\log q_{Fe}$	−2·60	−1·40	−0·83	−0·42	0·60

involved in Fig. 1, polymerisation (which is excluded on other grounds) being omitted, cannot alone account for the results. Changes in solvent activity must be considered.

Distribution of Ferric Chloride in Systems containing Methanol.—The distribution of hydrochloric acid in several of the three-component two-phase systems described in Table 5 goes through a maximum with increasing acid. The distribution of ferric chloride into such solvents was now studied in order to determine whether similar maxima appeared in its extraction. The solvent chosen for such a test was that given by 25 ml. of ethyl ether, 7·5 ml. of methyl alcohol, and 5 ml. of aqueous acid of different concentrations. It was first shown that the distribution coefficient of iron was independent of concentration below 0·002M-Fe. The iron distribution at the different acidities is given in Table 9, and a plot of $\log q_{Fe}$ against $\log [HCl]_o$ in Fig. 3. The iron extraction goes through a maximum when $[HCl]_o$ is a maximum. The logarithmic plot reveals that the values of $\log q$ on either side of the maximum lie on the same straight line, except at initial acidities greater than 8M.

Similar distribution maxima have been observed in the extraction of certain actinide and lanthanide complexes (Peppard, Gray, and Markus, *J. Amer. Chem. Soc.*, **1953**, **75**, 6063; Peppard, Foris, Gray, and Mason, *J. Phys. Chem.*, 1953, **57**, 294).

Our first attempt to explain this behaviour assumed an equilibrium in the organic phase between acid and ferric chloride: $FeCl_3 + HCl \rightleftharpoons FeCl_4H$, implying (Fig. 1) that more than one species was extracted. This is readily tested by measurement of the absorption spectrum of the extracted iron solutions at different acidities. The spectra obtained at acidities of 0·56, 1·20, and 5·65M-hydrochloric acid, *i.e.*, on both sides of the

TABLE 9. *Extraction of ferric ions from methanol-containing solvent systems.*

Solvent: 25 ml. of ether, 5 ml. of aqueous hydrochloric acid, of normality N, 7·5 ml. of methyl alcohol. Initial aqueous iron = 10^{-3}M.

N	0·122	0·232	0·329	0·378	0·458	0·572	0·680
$-\log [HCl]_{organic}$	2·25	1·99	1·85	1·77	1·73	1·59	1·55
$\log q_{Fe}$	−1·36	−1·04	−0·77	−0·64	−0·48	−0·29	−0·09
N	1·120	2·200	3·24	4·25	5·80	6·18	
$-\log [HCl]_{organic}$	1·45	1·35	1·39	1·38	1·50	1·61	
$\log q_{Fe}$	0·10	0·28	0·27	0·24	−0·06	−0·21	

maximum distribution, were identical even in so far that the extinction coefficients at maximum absorption varied insignificantly. Further, the relative absorption at different wavelengths was that to be expected for $FeCl_4^-$ (Friedman, *loc. cit.*). Thus only one spectroscopically distinct species is extracted. A second equilibrium in the organic phase which could control distribution is $FeCl_4^- + H^+ \rightleftharpoons HFeCl_4$. This equation, however, gives the wrong dependence of iron distribution upon acid concentration in the organic phase, for it is found that the former varies as $[HCl]_o^2$. The third possibility is that the distribution is partly dependent on equilibria such as those given and partly on change in partition coefficient due to changes in the activities of the solvent. The latter would account for the changing distribution of the hydrochloric acid as well as of the ferric chloride, for it has been shown that the former is dependent on the concentration of water in the organic phase (p. 1923). In this connection it is noteworthy that, at the acidities where the extraction of ferric chloride into the ethers begins to increase rapidly, the extraction of the acid also rises sharply.

A further test of the effect of solvent changes was now made. Ferric chloride was extracted into the solvent system formed from the three components, methanol (V ml.), ethyl ether (25 ml.), 2·78M-hydrochloric acid (5 ml.). As V is increased the system passes very close to the plait-point of the methanol–acid–ether system beyond which only one phase remains. The data are given in Table 10. As the amount of methanol is increased, the acidity of the aqueous phase falls and that of the organic phase increases, both approaching 0·2—0·4M. At the same time the distribution coefficient of water also

TABLE 10. *Extraction systems containing a varying amount of methanol but a constant amount of acid* [5·0 ml. of aqueous acid (2·78M); 25 ml. of ethyl ether; V ml. of methanol].

	Final acidity:		Final $[H_2O]$:	
V	lighter phase	heavier phase	lighter phase	q_{Fe}
0·0	—	2·40	0·35	0·06
2·5	0·0032	1·71	0·60	0·60
5·0	0·0085	1·25	1·00	2·11
6·5	0·0252	0·99	1·37	2·35
7·5	0·043	0·85	2·20	1·94
8·0	0·070	0·73	4·34	1·71
8·5	0·098	0·66	5·80	1·47
9·0	0·12	0·53	—	1·32

approaches unity. At the plait-point the distribution coefficients of all the species in the system must be unity (Part I). The manner in which the distribution coefficient for iron approaches this value is that it first increases to a value greater than unity and then falls towards unity. This maximum in distribution cannot be due to sequential equilibria, as

the ligand concentration in the aqueous phase is falling. The variations in distribution are due to "non-ideal" behaviour, *i.e.*, to changes in the activities of the solvents in the two phases.

Maxima in distribution coefficients have been observed in many other systems in circumstances which are not controlled by sequential equilibria. In particular, the experimental observations by Irving and Rossotti (*Analyst*, 1952, **77**, 801) do not lend themselves to such an interpretation. The fact that the metal involved is independent of the variation of distribution with acidity at higher acidities can only be explained in terms of changing partition coefficients, *i.e.*, non-ideal extraction conditions. However, in other cases unexpected changes in distribution with change of metal-ion concentration have been interpreted as arising from polymerisation in the aqueous phase (Herber *et al.*, *loc. cit.*; and see Part IV). In the authors' view it seems more probable that such depressions of extraction with rising cation concentration arise from the changing activity of the solvents (cf. MacKay, *Trans. Faraday Soc.*, 1952, **48**, 1103).

Experimental.—The concentration of acid in the organic phase in equilibrium with different aqueous acid concentrations was determined as follows: 25 ml. of aqueous acid were shaken with the same volume of organic solvent in a stoppered glass tube. Equilibrium was shown to be established in 10 min.; 10 ml. of the organic phase were then pipetted into a second tube containing 10 ml. of distilled water. After 10 minutes' shaking, effectively all the acid had been extracted into the aqueous layer; the partition coefficient of hydrochloric and hydrobromic acids is about 10^4, favouring the aqueous phase. As there was no measurable volume change during the second operation, the concentration of acid in the original organic layer was now given by that in the aqueous layer. The latter concentration was found by determining the conductivity by use of a probe-type conductivity cell of the usual simple design. The conductivity of acid corresponding to a given conductivity was then read off on a previously prepared calibration graph. The conductivity of the distilled water used was lower by a factor of ten than any of the readings used in compiling Table 1.

Conductivity of the ether layer. The ether layer was shown to have a well-defined conductivity after equilibration with aqueous hydrochloric acid by simple experiments using the conductivity cell and bridge as in the above experiments. It was suspected that the conductivity observed might be due, at least in part, to a layer of moisture on the glass supports of the platinum wires forming the conductivity cell. This was disproved by showing that the measured conductivity of the ether layer was dependent on the extent to which the wire electrodes were immersed in the ether. The conductivity was not directly proportional to the amount of acid in the ether, and we attribute the lack of correlation between these two qualities to the incomplete dissociation of the acid in the ether. It was for this reason that the acid in the ether layer was determined by the back-extraction described above.

Determination of ferric iron concentrations. Ferric concentrations were determined by the thiocyanate method. The details of our procedure followed those recommended by Sandell ("Colorimetric Analysis for Trace Metals," Interscience, New York, 1950, p. 363).

Determination of water content of ether layer. The usual Karl Fischer method was employed. Our technique differed only in a few minor respects from that of Smith, Bryant, and Mitchell (*J. Amer. Chem. Soc.*, 1939, **61**, 2407) and we prepared our reagents by their methods.

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INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

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The Extraction of Indium at Tracer Concentrations from Acid–Bromide Solutions into iso*Butyl Methyl Ketone.**

By H. Irving and F. J. C. Rossotti.

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A detailed study has been made of partition equilibria in the system indium–hydrobromic acid–*iso*butyl methyl ketone, ^{114}In being used as a tracer. At low metal concentrations (less than 10^{-5}M) only mononuclear species exist in the two phases. The acido-complex $HInBr_4$,aq. predominates in the organic phase at relatively high acidities, but other species such as $InBr_3$ and (in the presence of alkali-metal cations) salts or ion-pairs of the type $A^+InBr_4^-$ partition to a lesser extent. At high bromide-ion concentrations the partition of indium still favours the organic phase even when the hydrogen-ion concentration is low. Estimates have been made of the order of magnitude of relevant partition coefficients and equilibrium constants.

The precise nature of the species which passes on partition into the organic phase has seldom been established with certainty in the solvent extraction of inorganic salts. In some cases its composition has been determined by analysis on the macro-scale, though this provides no direct evidence of molecular complexity and may be misleading if a considerable amount of acid is co-extracted (cf., *inter al.*, Myers, Metzler, and Swift, *J. Amer. Chem. Soc.*, 1950, **72**, 3767; Nachtrieb and Fryxell, *ibid.*, 1949, **71**, 4035; Bock, *Z. anal. Chem.*, 1951, **133**, 110; Bock, Kusche, and Bock, *ibid.*, 1953, **138**, 167). At best, such analyses indicate only the bulk composition of the solute without distinguishing between a single compound and a mixture of several in approximately constant proportions.

In the present paper attempts are made to ascertain the nature of the extracted species in a particular system by detailed studies of partition equilibria. This approach has proved successful with inner complexes derived from the comparatively weakly acidic reagents 8-hydroxyquinoline (oxine) and cupferron (Dyrssen, *Svensk Kem. Tidskr.*, 1953, **65**, 43), dithizone (Irving, Bell, and Williams, *J.*, 1952, 356), or β-diketones (Connick and McVey, *J. Amer. Chem. Soc.*, 1949, **71**, 3182; Rydberg, *Acta Chem. Scand.*, 1950, **4**, 1503). Its extension to the extraction of inorganic species derived from anions of strong acids has been discussed in a previous general paper (Part I *). However, strict application of the equations deduced therein is limited to systems in which the solvent properties of the two phases do not alter with variations in the concentrations of any of the solutes, so that the constancy of partition coefficients and stability constants may be assumed.

The extraction of indium from a halogen acid offers possibilities for detailed studies, for it appears that the same type of substance is extracted by a wide variety of solvents (Part V *). However, measurements with hydrochloric acid are unsuitable since they demand high acidities if substantial amounts of indium are to be extracted. In these circumstances the magnitude of the distribution ratio, q, varies as a high power of the concentration of acid. This cannot be readily explained on the basis of the equations previously deduced (Part I), and the assumption that activities may be replaced by concentrations must break down in hydrochloric acid of the strength needed for extraction owing to the rapid increase of activity with concentration (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Co., New York, 1950). Indeed, the solution of hydrogen chloride in the aqueous phase brings about a substantial decrease in dielectric constant (Hasted, Ritson, and Collie, *J. Chem. Phys.*, 1948, **16**, 1) which will modify both the stability constants and the partition coefficients of all the dissolved species. Hydriodic acid is also unsuitable for the present purpose since its oxidation during the period of equilibration leads to uncertainties in the required concentrations of free hydrogen and of free iodide ions. The system *iso*butyl methyl ketone–

* This forms Part III of a group of papers of which Parts I and II are the preceding papers and Parts IV and V are the following papers.

hydrobromic acid was finally selected for detailed study, the choice of solvent resting upon its ability to extract indium to a considerable extent from acid concentrations less than molar, while, over the whole range of concentrations employed, changes in the mutual solubility of the two phases were negligible.

A full investigation of the system would require measurements of the distribution ratio

$$q = \frac{C_o}{C_w} = \frac{\text{Total concentration of indium in the organic phase}}{\text{Total concentration of indium in the aqueous phase}} \quad . \quad . \quad (1)$$

for the three cases where (i) the concentration of free indium ions, $[In^{3+}]$, is varied while the concentrations of free hydrogen ions, $[H^+]$, and of free bromide ions, $[Br^-]$, are held constant, (ii) $[H^+]$ is varied while $[In^{3+}]$ and $[Br^-]$ are both held constant, and (iii) $[Br^-]$ is varied while both $[In^{3+}]$ and $[H^+]$ are fixed. A useful check on deductions made from (ii) and (iii) can be carried out by varying the total concentration of halogen acid C_{HBr}, while $[In^{3+}]$ is held constant. By using ^{114}In in tracer quantities it is possible to keep the total concentration of this metal, C_M, very much smaller than the total concentrations of either hydrogen ion, C_H, or of bromide ion, C_{Br}. In these circumstances $[H^+] \approx C_H$, and $[Br^-] \approx C_{Br}$. There is, unfortunately, no way of ensuring the constancy of free indium ions, so that experiments based on procedures (ii) and (iii) can only be interpreted unequivocally where the results satisfy certain theoretical conditions, *viz.*, of being independent of $[In^{3+}]$. In the present work this difficulty was overcome by holding the total concentration of indium in the system constant at a value where measurements of distribution ratios by procedure (i) had proved them to be independent of C_M and hence of $[In^{3+}]$.

Experimental

Materials.—Radioactive indium (^{114}In; half-life 49 days) was obtained by irradiation to saturation of a known weight of "Specpure" indium wire (Johnson Matthey, Ltd.) in the nuclear reactor at A.E.R.E., Harwell. The irradiated wire was dissolved by first treating it with cold 5N-hydrobromic acid, gentle heat being applied after the initial vigorous reaction had abated. In some cases grey or red insoluble material was formed in the most concentrated solutions but, since clear colourless solutions were always obtained on further warming after the addition of a little hydrogen peroxide, such precipitates may have been due to bromides of a lower valency state of indium, or of a mixed valency state (cf. $TlBr_3 \equiv Tl[TlBr_4]$, and $Tl_3Br_3 = Tl_3TlBr_6$). A stock solution of $2{\cdot}5 \times 10^{-2}$M-indium in N-hydrobromic acid was made by quantitative dilution.

*iso*Butyl methyl ketone was distilled over potassium hydroxide and the fraction of b. p. range 114—116° was collected for use in the distribution experiments. Anhydrous sodium perchlorate was prepared by recrystallising an aqueous solution of the commercial hydrate at 90° and drying to constant weight at 115° (Fronaeus, "Komplexsystem Hos Koppar," Carl Bloms, Lund, 1948, p. 31). After two recrystallisations it was shown to be completely free from chloride and chlorate ions. Pure sodium bromide was available, and hydrobromic acid (free from bomine) was prepared freshly from time to time by redistilling an "AnalaR" sample. Other stock solutions of nitric acid, sodium nitrate, and potassium bromide and nitrate were made up from "AnalaR" reagents.

General Procedure.—The distribution ratio of indium [as defined by equation (1)] between *iso*butyl methyl ketone and a series of acid–bromide solutions was measured radiometrically by using ^{114}In as tracer. Aqueous phases were made up from appropriate dilutions of stock solutions of radioactive indium in hydrobromic acid, hydrobromic acid, or alkali bromide and nitric acid, being added together with alkali-metal nitrate or perchlorate to maintain a constant salt background. Series of experiments were performed in which the total concentrations of indium, hydrogen, or bromide ions were varied in turn, the other two concentration variables being held constant. All measurements refer to systems at equilibrium, the rate of attainment of equilibrium being measured by observing the increase of the apparent distribution ratio with time of shaking. Under the experimental conditions employed a shaking time of 2—3 min. was always sufficient for the attainment of equilibrium, and a standard time of 5 min. was adopted.

Neither phase was pre-saturated with the other before equilibrium in the distribution experiments. 20 Ml. of radioactive indium solution of known concentration in an acid–bromide

mixture of known composition and 20 ml. of *iso*butyl methyl ketone were pipetted into a 60-ml. Pyrex test-tube fitted with a ground-glass stopper. Equilibration was effected at room temperature (13° ± 3°) by mechanical shaking in a horizontal position for 5 min. at 150 cycles per min. B24 stoppers and test-tubes were carefully matched so that no losses occurred during the shaking. After equilibration, the tubes were placed upright, and the phases separated rapidly. Any globules of water entrapped at the air-ketone interface, or between the ketone and the walls of the tube, were dislodged by a sharp flick of the tube. The levels of the menisci were then noted on paper strips affixed to the outside of the tubes. After these had been emptied, washed, and dried, water was run in from a burette up to the marks to obtain the volumes of the organic and aqueous phases, V_0 and V, after equilibration. The standard deviation of such measurements was found to be of the order of ±1%. In the majority of the present experiments, the changes in phase volume on equilibration were not detectable within these limits.

The initial aqueous phase and the aqueous phase after equilibration were assayed radiometrically by means of 20th Century Electronics Ltd. G.M.6 liquid counters. As mass balances of 99·5 ± 4·8% were obtained in similar experiments in which aliquot parts of the organic phase were also analysed (Irving and Rossotti, *Analyst*, 1952, **77**, 801), the assumption of a 100% mass balance in the present work was considered to be justified.

Under comparable conditions of counting we have

$$C' : C : C_o = R' : R : R_o \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where C denotes the concentration of indium and R the counting rate, superscript dashes refer to aliquot parts of initial solutions (before equilibration), and the subscript o denotes the organic phase. For 100% mass balance

$$V'C' = VC + V_oC_o \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and combining equations (1), (2), and (3), we have

$$q = (V'R' - VR)/V_oR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The counting rates, R' and R, in this equation are corrected for the paralysis-time of the counting assembly, and for the background count (about 11 counts per min.). The duration of counting was always sufficient to give, at worst, a standard deviation of ±1%. Since the miscibility of the organic phase and aqueous phase was negligibly small and constant over the range of acidities used in the present investigation, no corrections were needed for self-absorption provided aliquot parts were assayed in the same G.M.6 tube. Correction for the decay of the 49-day ^{114}In was also unnecessary provided aliquots from any one experiment were assayed consecutively. For counting, 10 ml. of the equilibrium aqueous phase were transferred by pipette to the G.M.6 tube, great care being taken to avoid contamination by the (upper) ketonic phase. Aliquot portions of the aqueous phases, diluted where necessary, were also titrated with 0·1N-sodium hydoxide to determine the equilibrium acidity.

Partition Experiments.—All symbols used in the following Tables have been defined above. Within the limits of experimental error the initial and the final volumes of both aqueous and organic phases were 20·0 ml., unless there is a contrary statement.

1. *Rate of attainment of equilibrium.* For any one series of experiments this was investigated by shaking a number of tubes containing 20 ml. of *iso*butyl methyl ketone and 20 ml. of the same aqueous phase for varying lengths of time. Typical results are given in Table 1.

TABLE 1. *Rate of attainment of equilibrium of* 10^{-5}M-*indium in* 0·2N-*hydrobromic acid.*

t (min.)	0·5	2·0	3·0	5·0	10·0	30·0
q	0·935	1·043	1·067	1·076	1·067	1·071

2. *Dependence of distribution ratios upon the concentration of hydrogen ion, bromide ion, and hydrobromic acid.* Results are given in the following Tables.

3. *Analysis of organic extracts.* The organic extracts obtained by equilibration of solutions of low acidity were analysed in several cases for hydrogen, indium, and halide ions. A suitable aliquot portion of the organic phase was titrated with 0·1N-sodium hydroxide (thymol-blue as indicator), preliminary experiments having shown that the end-point was unaffected by the organic solvent. This gave the sum of hydrogen-ion concentration and three times the indium concentration. After acidification with dilute nitric acid, the bromide-ion concentration was determined by Volhard's method, control experiments having shown that the end-point was

TABLE 2. *Dependence of distribution on hydrogen-ion concentration.*

(*a*)	$[H^+]'$	0·80	0·50	0·20	0·05	0·0016		
	$[H^+]$	0·750	0·475	0·192	0·048	—		
	q	0·35	0·245	0·191	0·125	0·105		
(*b*)	$[H^+]'$	1·80	1·50	1·00	0·50	0·10	0·0116	0·0016
	$[H^+]$	1·51	1·27	0·873	0·433	0·085	—	—
	q	0·459	0·389	0·347	0·257	0·229	0·230	0·220

(*a*) Aqueous solutions for which [KBr] = 0·2M, and C_{In} = 7·92 × 10^{-5}M with variable amounts of nitric acid, the ionic strength being brought up to 1·0M with potassium nitrate. (*b*) Solutions for which [NaBr] = 0·2M and C_{In} = 7·92 × 10^{-5}M with variable amounts of nitric acid, the ionic strength being brought up to 2·0M with sodium nitrate.

TABLE 3. *Dependence of distribution ratio on bromide-ion concentration: potassium salts present.*

(*a*)	[KBr]	1·0	0·7	0·5	0·4	0·2	0·1
	q	1·31	0·650	0·426	0·330	0·105	0·0306
(*b*)	[KBr]	0·80	0·50	0·40	0·35	0·25	0·20
	q	8·22	2·81	1·22	0·620	0·313	0·191
	[KBr]	0·10	0·05				
	q	0·0307	0·0104				
(*c*)	[KBr]	3·84	1·92	1·00	0·96	0·50	0·30
	q	11·9	5·56	1·31	1·43	0·48	0·16
(*d*)	[KBr]	4·00	2·50	2·40	1·20	0·68	0·50
	q	18·7	30·0	39·6	20·5	6·55	3·21
	[KBr]	0·40	0·25	0·20	0·15	0·10	
	q	1·63	0·703	0·350	0·133	0·0662	

In the initial aqueous solutions C_{In} = 7·92 × 10^{-5}M in each case. In runs (*a*) and (*c*) the concentration of hydrogen ions at equilibrium was 0·0016N, in (*b*) it was 0·20N, and in (*d*) it was 0·26N. In runs (*c*) and (*d*) the ionic strength was not controlled, but in series (*a*) and (*b*) it was kept at 1·0M by appropriate additions of potassium nitrate.

TABLE 4. *Dependence of distribution ratio on bromide-ion concentration: sodium salts present.*

(*a*)	[NaBr] ...	1·00	0·75	0·50	0·25			
	q	3·23	1·85	0·790	0·203			
(*b*)	[NaBr] ...	0·80	0·50	0·25	0·10			
	q	10·0	2·52	0·405	0·0264			
(*c*)	[NaBr] ...	6·0	5·0	4·0	3·0	2·0	1·5	1·0	0·5
	q	92·0	160	162	53·5	25·3	11·4	3·23	0·602
(*d*)	[NaBr] ...	6·0	3·5	2·0	1·0	0·5	0·25	0·10	
	q	81·8	63·5	69·4	16·4	3·39	0·694	0·0853	
(*e*)	[NaBr] ...	1·00	0·70	0·50	0·35	0·20			
	q	28·3	10·4	4·27	1·64	0·347			

In all these solutions C_{In} = 7·92 × 10^{-5}M. In series (*a*) and (*c*) the concentration of hydrogen ions was 0·0016N, in series (*b*) and (*d*) it was 0·20N, and in series (*e*) 1·0N. The ionic strength was not controlled in series (*c*) and (*d*), but in series (*a*) and (*b*) it was maintained at 1·0M, and in series (*e*) at 2·0M by appropriate additions of sodium nitrate.

TABLE 5. *Dependence of the distribution ratio on the concentration of hydrobromic acid.*

	N'	N	V_e	V	q		N'	N	V_e	V	q
(*a*)	0·80	0·775	20·0	20·0	29·1	(*b*)	0·80	0·758	20·0	20·0	3·55
	0·60	0·57	20·0	20·0	7·61		0·60	0·550	20·0	20·0	1·15
	0·40	0·38	20·0	20·0	1·70		0·40	0·358	20·0	20·0	0·306
	0·20	0·20	20·0	20·0	0·210		0·20	0·175	20·0	20·0	0·0471
(*c*)	1·0	0·975	19·5	20·5	180						
	0·4	0·39	19·5	20·5	12·7						
	0·2	0·2	20·0	20·0	2·10						

In these experiments the concentration of indium was C_{In} = 5 × 10^{-6}M. In series (*c*) no attempt was made to control the ionic strength. In series (*a*) and (*b*) it was kept at 1·0M by appropriate additions of potassium nitrate and sodium perchlorate, respectively.

unaffected by the presence of indium or organic solvent. Indium was determined as previously described. Although the indium : bromine ratios were 1 : 4 within the limits of experimental error (see Table 7), the concentration of hydrogen ions, calculated on the assumption that 1 mole of indium reacts with 3 g.-equiv. of hydroxide ion, was found to be zero. Since the analytical method was certainly capable of detecting equivalent concentrations of hydrogen ions in the presence of 10^{-3} or 10^{-2}M indium (cf. Irving and Rossotti, Part IV, *loc. cit.*), it is concluded that alkali-metal complexes of the $InBr_4^-$ ion may undergo partition as well as the acido-species $HInBr_4$.

Dependence of Distribution Ratio upon Metal Concentration.—From the data presented in Table 6 it is clear that at each initial concentration of hydrobromic acid, N', either in the presence or in the absence of potassium nitrate, the distribution ratio, q, is independent of the total metal concentration in the range up to $C_{In} \sim 10^{-5}$M. At higher metal concentrations the distribution ratios decrease (Part IV).

TABLE 6. *Distribution of indium bromide species between hydrobromic acid and isobutyl methyl ketone at low metal concentrations.*

Initial acidity, N'	1·0		0·6		0·4	
Concn. of KNO_3, M	0·0		0·4		0·6	
$10^7 C_{In}$	q	$10^7 C_{In}$	q	$10^7 C_{In}$	q
10·0	185	5·00	7·60	5·00	1·73
50·0	180	50·0	7·61	50·0	1·70
111·0	180	244·0	7·68	295·0	1·72

It follows from the general treatment of partition equilibria given previously (Part I) that the derivative $(\partial \log q/\partial \log [In^{3+}])_{[HBr]}$ will only be zero when the (average) state of association is the same in both phases, and that under such conditions the derivative $(\partial \log q/\partial \log C_{In})_{[HBr]}$ will also be zero. Since experiments (cf. Table 6) establish the latter for indium concentrations less than about 10^{-5}M, it is reasonable to assume that at these low concentrations of metal all the species present are mononuclear. If this is the case, partition equilibria are independent of the concentration of free indium ions and hence, as found, of total metal concentration. In the following paper the presence of dinuclear indium complexes in the aqueous phases solutions is discussed : to avoid such complications indium concentrations of the order of 10^{-5}M were used throughout the present work. It will be assumed that the species In^{3+}, $InBr^{++}$, $InBr_2^+$, $InBr_3$, and $InBr_4^-$ exist in the aqueous phase together with the acido-complex $HInBr_4$. That no higher complexes exist in aqueous solution of hydrobromic acid of the strength employed here is supported by measurements of the stability constants (Carleson and Irving, *J.*, 1954, 4390, and refs. therein) and by comparison with the thoroughly investigated analogous system of Fe^{3+} and Cl^- (Gamlen and Jordan, *J.*, 1953, 1435).

Variation of Distribution Ratio with Hydrogen-ion Concentration.—Fig. 1 shows the results of measurements of distribution ratios for a series of solutions of constant total indium concentration in the presence of a constant excess of bromide ions, the concentration of hydrogen ions being varied. Nitric acid was used throughout as a source of hydrogen ions, preliminary experiments having shown that indium nitrate was not extracted into *iso*butyl methyl ketone. In series (*a*), 0·2M-potassium bromide was the source of bromide ions and the ionic strength was maintained at 1·0M by additions of potassium nitrate. In series (*b*), 0·2M-sodium bromide was used to provide bromide ions and the ionic strength was held at 2·0M by additions of sodium nitrate. In both cases $(\partial \log q/\partial \log [H^+])_{[Br^-]}$ tends to zero at relatively high values of pH, and towards unity at low values.

In such experiments it is pertinent to consider the possible hydrolysis of the indium ion, for competitive complex formation between bromide and hydroxyl ions might be expected to decrease extraction continuously towards zero at or before the point at which indium hydroxide is precipitated. If we accept Moeller's data (*J. Amer. Chem. Soc.*, 1941, **63**, 2625), precipitation of 10^{-5}M-indium halide solutions would occur at pH ~5. The present experiments were conducted at acidities greater than pH = 3 to give a margin of safety. The relative proportions of the species $InBr^{++}$ and $InOH^{++}$ at this pH in the presence of 0·2M-bromide ions can be estimated from the relevant stability constants.

Taking $[InBr^{++}]/[In^{3+}][Br^-] = 103$ and $[InOH^{++}]/[In^{3+}][OH^-] \sim 10^{10}$ (Carleson and Irving, *loc. cit.*, and refs. therein), we have $[InBr^{++}]/[InOH^{++}] \sim 200$, so that hydrolysis can be of only slight importance even at the highest pH used in this work.

If the species extracted into the organic phase contains no hydrogen (*e.g.*, $InBr_3$, $NaInBr_4$, or $KInBr_4$) the value of the derivative $(\partial \log q/\partial \log [H^+])_{[Br^-]}$ will be zero at comparatively low concentrations of bromide ion, but will approach unity if $HInBr_4$ has a high partition coefficient and is the predominant species in the organic phase. The present results confirm the predominance of $HInBr_4$ as the species extracted at relatively high acidities. They also demonstrate that at lower acidities one or more other species can undergo partition in a manner which is independent of hydrogen-ion concentration. These may be $InBr_3$, or an alkali-metal complex, $AInBr_4$, or a mixture of both. Although the differences in extraction from 1·0M-potassium salts or 2·0M-sodium salts containing 0·2M-bromide ion and a low hydrogen-ion concentration could be due to some activity effect,

FIG. 1.

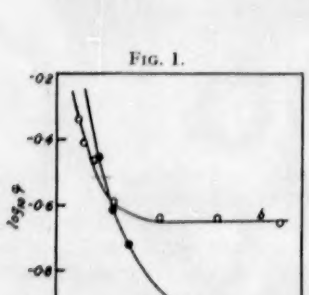

FIG. 2.

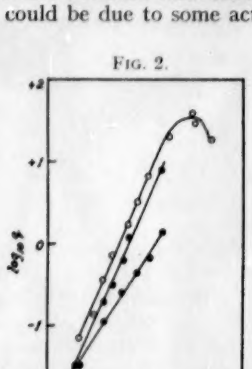

FIG. 1. *Dependence of distribution ratio upon hydrogen-ion concentration.*
For curve *a*, initial aqueous phases contained 0·2M-potassium bromide, and the ionic strength was made up to 1·0M with potassium nitrate. For curve *b*, they contained 0·2M-sodium bromide, and the ionic strength was made up to 2·0M with sodium nitrate.

FIG. 2. *Dependence of distribution ratio upon bromide-ion concentration.*
The hydrogen-ion concns. were 0·26N, 0·20N, and $1·6 \times 10^{-3}$N for open, full, and half circles, respectively. Potassium bromide was used as the source of bromide ions throughout, and the ionic strength was made up to 1·0M with potassium nitrate for the last two runs only.

the hypothesis that alkali-metal complexes can undergo partition is supported by recent work on the extraction of alkali-metal reineckates and per-rhenates into nitromethane (Friedman and Haugen, *J. Amer. Chem. Soc.*, 1954, **76**, 2060).

Variation of Distribution Ratio with Concentration of Bromide Ions.—Fig. 2 shows the results of measurements of distribution ratios for a series of solutions in which the concentration of indium and of hydrogen ions was the same, the concentration of bromide ion being varied. Nitric acid and potassium bromide were used as the source of these ions, and potassium nitrate was used to maintain an ionic strength of 1·0M in some experiments. Although the effect of the neutral salt is to decrease the extraction, the slopes of the plots of $\log q$ against $\log [Br^-]$ at constant hydrogen-ion concentration do not appear to be markedly affected by changes in the ionic strength of the medium. The values of the derivative $(\partial \log q/\partial \log [Br^-])_{[H^+]}$ are 1·6, 2·3, and 2·4 for $[H^+] = 0·0016$, 0·20, and 0·26 g.-ion/l. respectively. From the equations deduced previously (Part I, *loc. cit.*) it is clear that the value of this derivative would be $(3 - \bar{n})$ if $InBr_3$ were the extractable species, and $(4 - \bar{n})$ if the species $HInBr_4$ or $AInBr_4$ passes on partition. If, then, $\bar{n}$ is of the order of 1·6 for the whole range of bromide-ion concentrations explored, the experimental data favour the former hypothesis when $[H^+] \sim 10^{-3}$M, but the latter when $[H^+] \geqslant 0·1$M.

In a further series of experiments in which sodium bromide and nitrate replaced the corresponding potassium salts as the source of bromide ion and salt background respectively, comparable values of q were not greatly changed; but the values of the derivative $(\partial \log q/\partial \log [Br^-])_{[H^+]}$ were identical (2·3) both at $[H^+] = 0{\cdot}2$M and at 0·0016M. This is explicable if the species being extracted at low acidities (and $\bar{n} = 1{\cdot}6$) is either $HInBr_4$ or $NaInBr_4$. Only the latter hypothesis is consistent with observations on the dependence of q upon hydrogen-ion concentration discussed above. The feasibility of extracting indium–bromide species which do not contain hydrogen ions was further demonstrated by the successful extraction of indium from more concentrated bromide solutions at relatively high pH. Results collected in Table 7 show that the substantial amounts of indium ex-

TABLE 7. *Distribution of indium bromide species into* isobutyl methyl ketone *at low acidities.*

C_{KBr}	pH	$10^4 C_{In}$	q	$-\log C_e$	Analytical results for In : Br ratios
4·0	2·8	80·79	6·72	2·15	1 : 4·11 and 1 : 4·02
3·76	2·8	40·79	5·39	2·46	1 : 4·20 and 1 : 3·88
1·0	~4·2	2·528	0·876	3·60	
1·0	~4·2	25·03	0·497	2·60	
1·0	~4·2	250	0·250	1·60	

tracted were greater than the amount of hydrogen ion present to repress hydrolysis. Although analyses of the organic phases showed that the indium : bromine ratio was 1 : 4 within the limits of experimental error, no hydrogen was detectable. This result suggests that $KInBr_4$ was the predominant species extracted under these particular experimental conditions.

Variation of Distribution Ratio with Concentration of Hydrobromic Acid.—Fig. 3 shows how the distribution ratio for indium at a fixed total concentration of 5×10^{-6}M varies with the concentration of hydrobromic acid. In one series of experiments (curve *c*) no inert salt was added. In another (curve *a*) an ionic strength of 1·0M was maintained with potassium nitrate, with the result that distribution ratios were lower and the value of $(\partial \log q/\partial \log C_{HBr})$ was increased.

The possibility that nitrate ions were forming complexes competitively with indium in the aqueous phase and so reducing extraction was tested by replacing (potassium) nitrate by (sodium) perchlorate which might be expected to complex least strongly of all anions. Experimental results (Fig. 3, curve *b*) showed that partition into the organic phase is actually reduced still further by this substitution, although the value of the slope $(\partial \log q/\partial \log C_{HBr})$ is unaltered. This result disposes of the hypothesis of competitive complexing by nitrate ions but emphasises that additions of different "inert" salts will modify both (stoicheiometric) partition coefficients and stability constants and not necessarily to an equivalent extent. The marked increase in the value of $(\partial \log q/\partial \log C_{HBr})$ as the salt background is eliminated indicates the sensitivity of the results to the precise nature of the aqueous phase. There are innumerable examples of specific salt effects reported in the solvent extraction of inorganic materials (cf. Bock and Bock, *Z. anorg. Chem.*, 1950, **263**, 146; Jenkins and McKay, *Trans. Faraday Soc.*, 1954, **50**, 107). However, the possibility of the co-extraction of $KInBr_4$ and $NaInBr_4$ with partition coefficients lower than that of the acido-complex $HInBr_4$ is another relevant factor.

In the absence of alkali-metal cations the value of the derivative $(\partial \log q/\partial \log C_{HBr})$ is found to be 2·74 for free bromide-ion concentrations up to 1·0M. With salt backgrounds of 1·0M the value of this derivative is somewhat greater and equals 3·3 for hydrobromic acid concentrations below 0·5M in the presence of either potassium nitrate or sodium perchlorate. Under identical experimental conditions $(\partial \log q/\partial \log [Br^-])_{[H^+]} = 2{\cdot}3$. From the general treatment given in Part I the theoretical value of these derivatives would be $(5 - \bar{n})$ and $(4 - \bar{n})$, respectively, were $HInBr_4$ the predominant extractable species at relatively high acidities. This hypothesis is therefore confirmed, provided it can be shown that the degree of formation of the system is of the order $\bar{n} = 1{\cdot}7$—$2{\cdot}3$ for free bromide-ion concentrations in the range 0·1—0·5M.

Correlation of Partition and Stability Data.—The complexes which indium forms with bromide ions are comparatively weak, and by using an ion-exchange technique it has proved possible only to obtain the following over-all stability constants, $\beta_1 = 103$,

TABLE 8. *Percentage degrees of formation of indium bromide complexes, assuming* $\beta_1 = 103$, $\beta_2 = 1250$, $\beta_3 = 1900$, *and* $\beta_4 = 200$.

$-\log [Br^-]$	$\bar{n}$	α_0	α_1	α_2	α_3	α_4
2·0	0·60	46·38	47·78	5·75	0·88	$9·28 \times 10^{-4}$
1·0	1·60	3·90	40·20	48·40	7·42	0·0781
0·7	1·92	1·15	23·75	57·20	17·53	0·3690
0·5	2·13	0·46	14·83	56·45	27·35	0·9107
0·25	2·39	0·12	7·16	48·48	41·77	2·472
0·1	2·54	0·05	4·31	41·24	50·20	4·197
0·0	2·64	0·03	2·99	36·00	55·17	5·807

TABLE 9. *Corresponding values of q and* p_4K^H *for the distribution of* $HInBr_4$ *between isobutyl methyl ketone and hydrobromic acid.*

q	158·5	84·1	33·5	6·92	2·11
$10^{-3}p_4K^H$	2·73	2·53	2·41	2·40	2·86

FIG. 3.

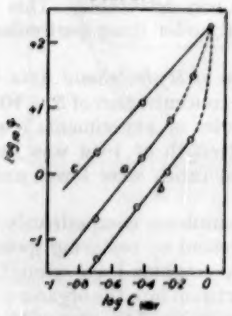

FIG. 4.

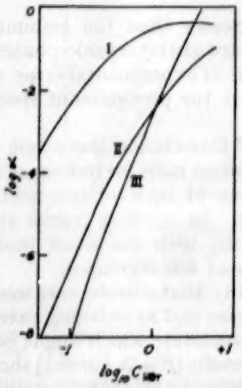

FIG. 3. *Dependence of distribution ratio upon hydrobromic acid concentration.* The ionic strength was made up to 1·0M with potassium nitrate and with sodium perchlorate for curves *a* and *b*, respectively. No salt background was used for curve *c*.

FIG. 4. *The degree of formation of some indium bromide complexes.* I, $InBr_3$; II, $InBr_4^-$; III, $HInBr_4/K^H$. The ordinate of the curve for $HInBr_4$ is displaced by $\log K^H$.

$\beta_2 = 1250$, and $\beta_3 = 1900$, which are valid for a medium of ionic strength 0·7M (perchloric acid) at 20° (Carleson and Irving, *loc. cit.*). These correspond to step-formation constants of $K_1 = 103$, $K_2 = 12·1$, and $K_3 = 1·5$. Since the ratio K_n/K_{n-1} is approximately 8, we may assume that $K_4 < 0·2$, a value which may be greatly overestimated if the trend of values resembles that for the ferric chloride complexes (Gamlen and Jordan, *loc. cit.*). The degree of formation of individual complexes, $\alpha_n = [InBr_n^{3-n}]/C_{In}$, and the average ligand number, $\bar{n}$, have been calculated for various concentrations of free bromide ion on the assumption that $\beta_4 = 200$. Table 8 shows that, even at the highest concentation of free bromide ion (1M) used in the extractions, the species $InBr_4^-$ is a minor constituent of the aqueous phase. Unless, therefore, the acido-complex is a very weak acid, which appears unlikely (cf. ferrocyanic acid; Nekrassov and Zotov, *J. Appl. Chem. U.S.S.R.*, 1941, **14**, 264; cf. *Chem. Abs.*, 1941, **35**, 1834), its partition coefficient, p_4, must be very large. The magnitude of the product p_4K^H (where $K^H = [HInBr_4]/[H^+][InBr_4^-]$) can be computed from the experimental data for media from which alkali cations are absent if it is postulated

that only the uncharged species $HInBr_4$ and possibly $InBr_3$ are extracted. It then follows that

$$q = p_3\alpha_3 + p_4\alpha_4 K^{H}[H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Using values of q, and corresponding values of α_3 and α_4 from Table 8, we can set up simultaneous equations and solve for p_3 and p_4K^{H}. It is at once evident that p_3 is negligibly small, *i.e.*, that the extraction of indium tribromide can be neglected in comparison with that of acido-species, $HInBr_4$, under conditions of high acidity. Table 9 gives the results of these computations which lead to a mean value of $p_4K^{H} = 2600 \pm 180$. Naturally any estimate of this product will depend upon the value of α_4 used in its calculation, and this in turn depends upon values taken for the stability constants. The possible effect of underestimating the value of K_2 and overestimating the value of K_4 is shown in Table 10. Although the changes make very little ifference to values of $\bar{n}$ at corresponding concen-

TABLE 10. *Percentage degrees of formation of indium bromide complexes, assuming* $\beta_1 = 114$, $\beta_2 = 2270$, $\beta_3 = 4450$, *and* $\beta_4 = 89$.

$-\log[Br^-]$	$\bar{n}$	α_0	α_1	α_2	α_3	α_4
2·0	0·68	42·18	48·08	9·57	0·19	$5{\cdot}54 \times 10^{-4}$
1·0	1·77	2·53	28·82	57·38	11·25	0·025
0·7	2·07	0·67	15·16	60·39	23·67	0·093
0·5	2·26	0·25	8·89	55·96	34·69	0·22
0·25	2·47	0·06	4·05	45·34	49·98	0·56
0·1	2·58	0·03	2·39	37·80	58·85	0·93
0·0	2·65	0·01	1·65	32·78	64·27	1·28

Corresponding values of q and p_4K^{H} *calculated with these alternative stability constants.*

q	84·1	33·5	6·92	2·11	0·299
$10^{-4}p_4K$	1·14	1·085	1·00	1·035	1·095

trations of free bromide ions, yet values of α_4 are reduced from two- to four-fold, and computed values of p_4K^{H} now have a mean value of 10,700 $\pm$ 500. That there is no serious drift in values of p_4K^{H} calculated in Tables 9 and 10 suggests that the general treatment cannot be seriously at fault and places the value of this product as of the order 10^3—10^4. A similar treatment of published data for the extraction of ferric chloride from hydrochloric acid shows that the extraction of the species $HFeCl_4$.aq. is substantial although the ion $FeCl_4^-$ forms only a minor constituent of the aqueous phase at moderate acidities.

The variation of α_3 (the fraction of the total indium present as $InBr_3$ in the aqueous phase) and of α_4 (the fraction present as $InBr_4^-$) with changes in the concentration of bromide ion is shown as a double logarithmic plot in Fig. 4. These data are calculated by using the stability constants quoted in Table 8. The product $\alpha_4[H^+]$ is proportional to the concentration of acido-complex and its variation with the total concentration of hydrobromic acid is also shown as a double logarithmic plot in Fig. 4.

It will be noted that the curvature of all the plots is slight over the range of concentrations, *viz.*, $0{\cdot}1 < [Br^-] < 1{\cdot}0$M, used in the present extraction studies. From the data calculated in Tables 8 and 10, values of $\bar{n}$ are seen to be comparatively insensitive to moderate changes in values adopted for stability constants over the same range of bromide-ion concentrations. Use of the preferred set of data (Table 8) shows $\bar{n}$ to increase from 1·6 to 2·64 as $[Br^+]$ increases from 0·1 to 1·0M. The mean value of 2·12 agrees well with the value, $\bar{n} = 2{\cdot}26$, deduced from the experimental value $(\partial \log q/\partial \log [HBr]) = 5 - \bar{n} = 2{\cdot}74$ found in this range for a medium containing no alkali-metal cations. The agreement again justifies the application of the idealised equations deduced in our general treatment (Part I, *loc. cit.*) to the solvent extraction of indium bromide.

For media which contain alkali-metal cations the experimentally determined values for $(\partial \log q/\partial \log [Br^-])$ when $[H^+] = 0{\cdot}0016$M, for $(\partial \log q/\partial \log [Br^-])$ when $[H^+] = 0{\cdot}2$M, and for $(\partial \log q/\partial \log [HBr])$, are 1·6, 2·3, and 3·3, respectively. These may be compared with the values of 1·4, 2·4, and 3·4 for $(\partial \log \alpha_3/\partial \log [Br^-])$, $(\partial \log \alpha_4/\partial \log [Br^-])$, and $(\partial \log \alpha_4[H^+]/\partial \log [HBr])$ found at a free ligand concentration of $[Br^-] = 0{\cdot}1$M, which also corresponds to the degree of formation of the system of $\bar{n} = 1{\cdot}6$. This correspondence with

the average ligand number obtaining at the *lowest* free-ligand concentrations used in the actual extractions suggests that some additional factor is operating to make extraction increase at a greater rate with bromide concentration than predicted theoretically. The marked increase in the value of the derivative $(\partial \log q/\partial \log C_{HBr})$ as the salt background is eliminated (Fig. 3) suggests that some specific-ion effect may be operative, and that activity coefficients were not adequately held constant in the aqueous phase, the nature of which changes substantially over the range of extraction conditions. Alternatively, the estimated value of β_4 may be seriously at fault : it must also be emphasised that the experimental values of β_1, β_2, and β_3 correspond to a different ionic strength (0·7M-perchloric acid) and a slightly different temperature (20°). It is, however, worth considering whether it is possible to interpret the values of distribution ratios in the presence of varying salt backgrounds on the assumption that the alkali-metal complexes $AInBr_4$ (A = Na or K) are co-extracted.

Equation (5) may be extended as follows :

$$q = p_3\alpha_3 + p_4\alpha_4K^H[H^+] + p_A\alpha_4K^A[A^+] \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where p_A is the partition coefficient and K^A the stability constant of the species $AInBr_4$. In Table 11 results of calculations are shown on the assumption (i) that only $InBr_3$ and $HInBr_4$ are co-extracted, and (ii) that only $HInBr_4$ and $AInBr_4$ are co-extracted. As expected, there are substantial drifts in the calculated values of the parameters though these are greater for a background of sodium nitrate than one of potassium nitrate, and

TABLE 11. *Calculations from data for the extraction of indium from hydrobromic acid solutions containing alkali cations.*

	Potassium nitrate				Sodium nitrate			
$-\log [Br^-]$	p_3	p_4K^H	p_4K^H	p_KK^K	p_3	p_4K^H	p_4K^H	$p_{Na}K^{Na}$
0·7	0·572	123	150	26·7	0·656	115	145	30·8
0·5	0·765	174	197	22·7	1·06	189	220	31·1
0·25	1·22	319	330	20·1	2·53	345	388	41·5
0·1	1·99	464	485	20·4	4·56	515	570	52·0
0·0	2·44	600	600	21·6	7·1	700	700	65·4
Assumption	(i)		(ii)		(i)		(ii)	

greater on assumption (i) than on assumption (ii). It appears that the extraction of the alkali-metal complex $AInBr_4$ relative to that of the tribromide is greater in systems containing sodium than in those containing potassium ions, a conclusion in keeping with deductions made above from values of $(\partial \log q/\partial \log [Br^-])$. Similar calculations with the alternative sets of stability constants used in Table 10 gave values of the various parameters which showed very much larger drifts, though the order $p_4K^H > p_{Na}K^{Na} > p_KK^K \gg P_3$ remained unchanged. Our calculations of α_3 and α_4 have assumed that the degrees of formation of the complexes $InBr_3$ and $InBr_4^-$ are unaffected by the presence of hydrogen ions or alkali-metal ions, *i.e.*, that K^H and K^K are small. The departures from the behaviour predicted theoretically may be due to extensive association of proton or alkali metal with the ion $InBr_4^-$ in the aqueous phase, or to failure to hold activity coefficients constant, or to real variations in the values of the (stoicheiometric) partition coefficients and stability constants under the range of experimental conditions.

Discussion.—The present experiments emphasise some of the fundamental difficulties encountered in examining the solvent extraction of inorganic salts. When studying the extraction of a metal as a stable inner complex, ML_n, of a weak monobasic acid, HL, the extractability can be investigated over a wide range of pH or HL. Activity coefficients can be held reasonably constant if there is a sufficient salt background in the aqueous phase, for only an uncharged species passes on partition into the organic phase. Other simplifying features of such systems are the extraction of a single species of such high stability that, at low free-ligand concentrations, a study of the derivatives $(\partial \log q/\partial \log [H^+])_{[M]}$ or $(\partial \log q/\partial \log [L])_{[H^+]}$ gives immediately and unequivocally the nature of the dissolved species. Furthermore, there is no evidence as yet of complications due to polynuclear species (cf. Part IV).

In comparable studies of the solvent extraction of inorganic salts the effect of acids in increasing phase miscibility sets an upper limit to the concentration of ligand which can be reached experimentally (Parts I, II, and V). But much lower concentrations may be desirable if phase compositions are not to be drastically modified. The species extracted may be a minor constituent of the mixture of complexes present in the aqueous phase—as we have demonstrated in the present instance—and present in amounts sufficient to give a readily measurable distribution ratio only at high ligand concentrations. Attempts to hold activity coefficients constant in the aqueous phase by providing a still higher concentration of a neutral salt (*e.g.*, an alkali-metal nitrate or perchlorate) may not be entirely effective in concentrations where the Debye–Hückel theory does not apply and where specific salt effects may dominate the situation. Furthermore, owing to their high tendency to solvation, alkali-metal salts may further reduce the activity of water in the aqueous phase, so hindering the extraction of hydrated species. Partition coefficients and stability constants will change in consequence of changes in the characteristics of the phase. The cations of the added " neutral " salt may compete with protons and form ion-pairs which also undergo partition. Its anions may form complexes in competition with the metal being studied and change its extractability.

In order to make any reliable deductions from variations in extractability with, *e.g.*, pH and free-ligand concentration, they must be varied over sufficiently wide limits, other factors being held constant. Although we have indicated above why attempts to do this may introduce unexpected complications, yet a consistent picture of the extraction of indium into *iso*butyl methyl ketone results from the assumption that more than one species is co-extractable. Provided $[H^+] > 0{\cdot}1$M, the predominant species is $HInBr_4$.aq., but at lower acidities the extraction of both indium tribromide and the alkali-metal complexes $NaInBr_4$ and $KInBr_4$ may become significant. Although the Raman spectrum of $InBr_4^-$ has been found in organic extracts from both acid and essentially neutral solutions of indium and bromide ions (Woodward and Bill, to be published), the possible presence of some indium tribromide could be not disclosed by this technique.

It has generally been assumed that only an acido-complex is extracted from solutions of tervalent metals in halogen acids, although observations which show that other species may play an important rôle are to be found in the literature. Thus a close analogy to the present system is found in the extraction of thiocyanates of many metals where the partition of both the normal salt $M(CNS)_3$ and the complex salts $(NH_4)_3M(CNS)_6$ into diethyl ether ($M = Fe^{3+}$, Al^{3+}, Ga^{3+}, and In^{3+}) has been demonstrated under different experimental conditions (Bock, *loc. cit.*). Gold has been extracted from bromide solutions into *iso*butyl methyl ketone and into ethyl acetate (McBryde and Yoe, *Analyt. Chem.*, 1948, **20**, 1094), and gallium from chloride solutions into ethyl methyl ketone (Milner, Wood, and Woodhead, *Analyst*, 1954, **79**, 272) in the absence of halogen acid. Nekrassov and Ovskyankina (*J. Gen. Chem. U.S.S.R.*, 1941, **11**, 573; *Chem. Abs.*, 1941, **35**, 7266) have shown that ferric chloride is extracted from solutions containing no great excess of hydrogen ions. Equilibrium in these systems was interpreted in terms of the simultaneous extraction of the species $H[FeCl_4(H_2O)_2]$ and $H[FeCl_3(OH)(H_2O)_2]$, but there appears to be no convincing evidence for not formulating the latter simply as $FeCl_3$.aq. In such systems where two or more species may be coextracted it is quite clear that the relative proportions passing into the organic phase will depend upon their relative partition coefficients and will be very sensitive to the relevant concentration variables of the aqueous phase as shown by equation (6). Conditions under which one or other species predominates in the organic extract may be accessible to experimental study, but the range where their contributions to the total extraction approach equality is likely to be too restricted for investigation.

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The Inorganic Chemistry Laboratory,
South Parks Road, Oxford.

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*The Extraction of Indium at Macro-concentrations from Hydrobromic Acid into isoButyl Methyl Ketone and Diethyl Ether.**

By H. Irving and F. J. C. Rossotti.

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Tracer studies of partition equilibria in the system indium bromide–hydrobromic acid–*iso*butyl methyl ketone have been extended to higher metal concentrations. The observed decrease in the distribution ratio is interpreted in terms of the formation of dinuclear indium–bromide complexes which are extracted to a negligible extent compared with the acido-complex $HInBr_4.aq$. With diethyl ether the distribution ratio increases with metal concentration and the acido-complex is shown by analysis to be extracted as the decahydrate.

It is well known that the partition of ferric iron between hydrochloric acid and diethyl or di*iso*propyl ether increasingly favours the organic phase as the concentration of metal is raised (Dodson, Forney, and Swift, *J. Amer. Chem. Soc.*, 1936, **58**, 2573). Tervalent gold (Mylius and Huttner, *Ber.*, 1911, **44**, 1315; McBryde and Yoe, *Analyt. Chem.*, 1948, **20**, 1094) and gallium (Nachtrieb and Fryxell, *J. Amer. Chem. Soc.*, 1949, **71**, 4035) behave in a similar manner in these solvents. The attempt to interpret such behaviour in terms of an increase in the activity of the metal halide species in the aqueous phase (Nachtrieb and Fryxell, *ibid.*, 1948, **70**, 3552) was disproved by its originators and it now appears to be accepted that the phenomenon results from some form of association of the species in the organic phase, or from a decrease in its activity due to this or other causes (cf. Myers, Metzler, and Swift, *ibid.*, 1950, **72**, 3767; Nachtrieb and Fryxell, *ibid.*, 1952, **74**, 897).

We have now found an example of the converse phenomenon. For, although tracer studies of partition equilibria in the system indium bromide–hydrobromic acid–*iso*butyl methyl ketone (Part III*) showed that the distribution ratio defined by

$$q = \frac{C_o}{C_w} = \frac{\text{total concentration of indium in organic phase}}{\text{total concentration of indium in aqueous phase}} \quad . \quad . \quad . \quad (1)$$

was independent of metal concentration up to $\sim 10^{-5}$M, yet, when the measurements were extended to higher concentrations of indium, the distribution ratio for any given constant concentration of hydrobromic acid was found to decrease.

Experimental

Materials.—Inactive indium bromide was prepared by dissolving a known weight of pure indium (Johnson Matthey, Ltd.) in the calculated quantity of 5N-hydrobromic acid, free from bromine. The solution was gently evaporated to small bulk and kept in a vacuum-desiccator over potassium hydroxide for some weeks. The composition of the pure white product was confirmed by gravimetric determination of indium as oxide (Moser and Siegmann, *Monatsh.*, 1930, **55**, 16) and of bromine as silver bromide; a stock solution of strength 0·2M was prepared. A $2{\cdot}5 \times 10^{-3}$M stock solution of radioactive indium bromide in N-hydrobromic acid was prepared from ^{114}In, and *iso*butyl methyl ketone was purified as described previously (Part III). Commercial diethyl ether was purified and freed from peroxides as described by Weissberger and Proskauer ("Organic Solvents," Oxford, 1935). "AnalaR" potassium nitrate was used to provide a salt background in some experiments.

Partition Experiments.—The distribution ratios of indium, as defined by equation (1), between *iso*butyl methyl ketone and hydrobromic acid were studied as a function of total indium concentration, C_{In}, at a number of different initial acid concentrations, N'. For a series of partition experiments solutions were made up identical in their content of hydrobromic acid and of radioactive indium bromide (10^{-5}—10^{-7}M) but which differed in their content of inactive indium (0—10^{-2}M). In some series of measurements the ionic strength was made up to 1·0M by

* This forms Part IV of a group of papers of which Parts I, II, III are the preceding papers and Part V the following paper.

appropriate additions of potassium nitrate. Portions of these solutions (20 ml.) were equilibrated with equal volumes of *iso*butyl methyl ketone in 60-ml. Pyrex stoppered tubes by shaking for 5 min. in a horizontal position at 150 cycles per minute at room temperature (13° ± 3°). The phases were then allowed to separate with the tubes in a vertical position. With systems containing relatively high concentrations of indium (~10^{-2}M) the ketonic layers were cloudy, and times up to 1 hr. had to be allowed before the phases had completely separated. The volumes V_o and V of the organic and the aqueous phase respectively after equilibration were measured, and radiometric determinations of indium were carried out as already described (Part III). The equilibrium acidity, N, was determined by titrating diluted aliquot portions of the aqueous phase with 0·1N-sodium hydroxide.

Results of the measurements are summarised in Tables 1 and 2, the symbols being those defined above. Unless the contrary is stated the equilibrium volumes $V_o = V = 20$ ml. within the limits of experimental error.

TABLE 1. *Variation in distribution ratio of indium between hydrobromic acid and isobutyl methyl ketone for different indium concentrations. (No added salts.)*

C_{In}	$-\log C_o$	$-\log C$	q	C_{In}	$-\log C_o$	$-\log C$	q
			(*a*) $N' = N = 0{\cdot}20$N-HBr.				
$8{\cdot}008 \times 10^{-3}$	2·156	1·138	0·0956	$5{\cdot}145 \times 10^{-5}$	4·575	4·605	1·07
$1{\cdot}008 \times 10^{-2}$	3·029	2·039	0·102	$3{\cdot}168 \times 10^{-5}$	4·740	4·870	1·35
$1{\cdot}079 \times 10^{-2}$	3·670	3·063	0·247	$8{\cdot}33 \times 10^{-6}$	5·266	5·537	1·87
$4{\cdot}316 \times 10^{-4}$	3·932	3·502	0·372	$3{\cdot}168 \times 10^{-6}$	5·668	5·991	2·10
$7{\cdot}92 \times 10^{-4}$	4·436	4·371	0·862	$7{\cdot}92 \times 10^{-7}$	6·266	6·603	2·18
			(*b*) $N' = 0{\cdot}40$N-HBr; $N = 0{\cdot}39$N-HBr; $V_o = 19{\cdot}5$ ml.; $V = 20{\cdot}5$ ml.				
$1{\cdot}00 \times 10^{-2}$	2·604	2·134	0·336	$5{\cdot}145 \times 10^{-5}$	4·346	5·148	6·34
$5{\cdot}50 \times 10^{-3}$	2·750	2·440	0·485	$6{\cdot}444 \times 10^{-6}$	5·222	6·242	10·5
$1{\cdot}001 \times 10^{-3}$	3·392	3·312	1·04	$5{\cdot}00 \times 10^{-6}$	5·325	6·429	12·7
$1{\cdot}011 \times 10^{-4}$	4·089	4·679	3·86	$2{\cdot}40 \times 10^{-6}$	5·647	6·707	11·5
$5{\cdot}377 \times 10^{-5}$	4·324	5·136	6·48	$6{\cdot}00 \times 10^{-7}$	6·245	7·349	12·7
			(*c*) $N' = 1{\cdot}00$N-HBr; $N = 0{\cdot}975$N-HBr; $V_o = 19{\cdot}5$ ml.; $V = 20{\cdot}5$ ml.				
$2{\cdot}50 \times 10^{-2}$	1·682	2·332	4·46	$1{\cdot}111 \times 10^{-5}$	4·946	7·196	180
$2{\cdot}503 \times 10^{-3}$	2·626	3·726	12·6	$5{\cdot}00 \times 10^{-6}$	5·539	7·289	180
$2{\cdot}528 \times 10^{-4}$	3·596	5·286	49·4	$2{\cdot}50 \times 10^{-6}$	5·594	7·774	152
$5{\cdot}145 \times 10^{-5}$	4·283	6·363	119	$1{\cdot}00 \times 10^{-6}$	5·991	8·261	185
$2{\cdot}778 \times 10^{-5}$	4·560	6·629	114				

TABLE 2. *Variation of distribution ratio with indium concentration for extraction into isobutyl methyl ketone from hydrobromic acid in a medium of ionic strength* 1·0M.

C_{In}	$-\log C_o$	$-\log C$	q	C_{In}	$-\log C_o$	$-\log C$	q
			(*a*) $N' = N = 0{\cdot}20$N-HBr.				
$8{\cdot}009 \times 10^{-3}$	2·416	1·118	0·0479	$7{\cdot}92 \times 10^{-5}$	4·951	4·168	0·165
$4{\cdot}004 \times 10^{-3}$	2·575	1·427	0·0712	$3{\cdot}168 \times 10^{-5}$	5·294	4·575	0·191
$8{\cdot}049 \times 10^{-3}$	3·175	2·132	0·0906	$7{\cdot}920 \times 10^{-5}$	5·859	5·184	0·212
$1{\cdot}079 \times 10^{-3}$	3·885	3·023	0·137	$3{\cdot}168 \times 10^{-6}$	6·246	5·585	0·218
$1{\cdot}079 \times 10^{-4}$	4·802	4·036	0·171				
			(*b*) $N' = 0{\cdot}40$N-HBr; $N = 0{\cdot}375$N-HBr.				
$2{\cdot}50 \times 10^{-3}$	2·300	1·700	0·251	$2{\cdot}945 \times 10^{-5}$	4·730	4·966	1·72
$2{\cdot}505 \times 10^{-3}$	3·044	2·796	0·565	$5{\cdot}00 \times 10^{-6}$	5·502	5·733	1·70
$1{\cdot}002 \times 10^{-3}$	3·352	3·254	0·805	$5{\cdot}00 \times 10^{-7}$	6·500	6·736	1·73
$2{\cdot}545 \times 10^{-4}$	3·836	3·964	1·34				
			(*c*) $N' = 0{\cdot}60$N-HBr; $N = 0{\cdot}563$N-HBr.				
$2{\cdot}00 \times 10^{-3}$	2·067	1·942	0·749	$2{\cdot}444 \times 10^{-5}$	4·665	5·551	7·68
$2{\cdot}004 \times 10^{-3}$	3·179	3·487	2·03	$5{\cdot}00 \times 10^{-6}$	5·355	6·237	7·61
$8{\cdot}016 \times 10^{-4}$	3·223	3·691	2·95	$5{\cdot}00 \times 10^{-7}$	6·355	7·237	7·60
$2{\cdot}044 \times 10^{-4}$	3·783	4·402	4·16				

Extraction of Indium from Hydrobromic Acid Solutions into Diethyl Ether.—A few experiments were performed to study the variation in distribution ratio with indium concentration. No alkali nitrate was added. Typical results are given in Table 3.

Analysis of the Organic Extracts.—A number of solutions in which the total indium concentration was of the order of 10^{-2}M were equilibrated with *iso*butyl methyl ketone or diethyl

ether, and the organic phases analysed for hydrogen, indium, and bromine by the methods described by Irving and Rossotti (Part III). In these experiments, however, it was necessary to subtract a small blank from the titre of sodium hydroxide to allow for the amount of hydrobromic acid extracted in the absence of indium.

TABLE 3.

N'	N	C_{In}	q	C_{In}	q
2·0	1·80	10^{-4}	1·38	0·1	3·76
3·0	2·60	10^{-4}	11·9	0·05	32·4
4·0	3·24	10^{-4}	44·2	0·1	139

The diethyl ether extracts were also analysed for water co-extracted with the indium by the Karl Fischer method, using a micro-titration apparatus of the type described by Bonner (*Analyst*, 1946, **71**, 483). Direct titrations were carried out in an atmosphere of nitrogen, the dead-stop end-point being used with the following modification. The indium content of an aliquot part of ethereal phase containing a conveniently measurable quantity of water being known from preliminary experiments, sufficient of a 0·5M-solution of 8-hydroxyquinoline in dry methanol to afford a tenfold excess was first titrated to the Karl Fischer end-point. The known volume of ethereal phase was then added, and the additional water titrated to the same end-point. Finally, the Karl Fischer reagent was standardised in the presence of the indium trisoxine complex. The amount of water present in diethyl ether after equilibration with hydrobromic acid of the desired concentration in the absence of indium was then determined and subtracted from the total concentration previously found. Diethyl ether was scrupulously freed from peroxides which react with the Karl Fischer reagent. The latter was of B.D.H. laboratory grade. Other materials were prepared as recommended by Mitchell and Smith ("Aquametry," Interscience Press, New York, 1948). The results are summarised in Table 4.

TABLE 4. *Analyses of organic extracts.*

(*a*) iso*Butyl methyl ketone.*

Composition of initial aqueous phase, moles/l.			Analytical ratios			
$InBr_3$	HBr	KNO_3	H_2O	H	In	Br
0·020	0·60	0·40	—	1·00	1·00	3·94
0·020	0·60	0·40	—	1·10	1·00	4·08
0·020	0·60	0·40	—	1·02	1·00	4·02
0·020	0·60	0·40	—	1·02	1·00	4·02
0·025	0·40	0·60	—	1·01	1·00	4·00
0·025	0·40	0·60	—	1·02	1·00	3·80
			(*b*) *Diethyl ether.*			
0·10	2·0	—	10·0	0·92	1·00	3·96
0·05	3·0	—	10·0	1·00	1·00	4·16
0·10	4·0	—	9·45	1·12	1·00	4·10

Variation of Distribution Ratio with Metal Concentration in iso*Butyl Methyl Ketone Systems.*—Fig. 1, curve 1, shows how the distribution ratio, q, varies for the extraction of indium from an equilibrium concentration of 0·975M-hydrobromic acid at different total metal concentrations. The curves for extraction from equilibrium concentrations of 0·20 and 0·39M-hydrobromic acid (not reproduced here; data in Table 1) are strikingly similar and can be superimposed by a vertical displacement. Irrespective of the concentration of hydrobromic acid there is a range up to a total metal concentration of $C_{In} \sim 10^{-5}$M over which the distribution ratio is independent of metal concentration (cf. Part III). At higher metal concentrations the distribution ratio steadily decreases. In experiments at the lowest acidity (0·2M) a second region of almost constant distribution ratio is suggested by the experimental results. This may not be significant, for the addition of indium bromide in macro-concentration will have increased the concentration of free bromide ion and also the ionic strength. On the other hand, the possibility that a dinuclear indium–bromide complex is formed at high metal concentrations (see p. 1945) and has a small but significant partition coefficient cannot be excluded.

So long as indium is present only in small concentrations, the ionic strength in the aqueous phase is effectively that of the hydrobromic acid; hence, the activity coefficients

remain constant (though different) in the three sets of experiments. Any attempt to explain the variations in q shown in Fig. 1 in terms of changes in the activity coefficient of the species extracted into the organic phase must explain why it is constant below 10^{-5}M, but increases markedly above this concentration. Not only is the magnitude of the change improbably large, but it is of opposite sign to that found in measurements of the activity of a similar solute, *viz.*, the ferric chloride–hydrochloric acid complex in *iso*propyl ether (Nachtrieb and Fryxell, *loc. cit.*). In the present paper we postulate that activity coefficients in the aqueous phase and (stoicheiometric) partition coefficients remain constant and explore the logical deductions which follow from an application of the law of mass action to the partition equilibria. Neglecting, then, any variations in activity in the organic phase, the observed variations in distribution ratio may be interpreted as arising from some form of association in the aqueous phase.

FIG. 1.

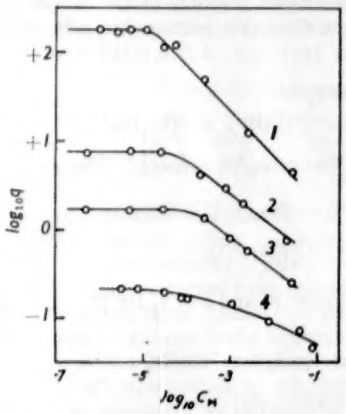

FIG. 2.

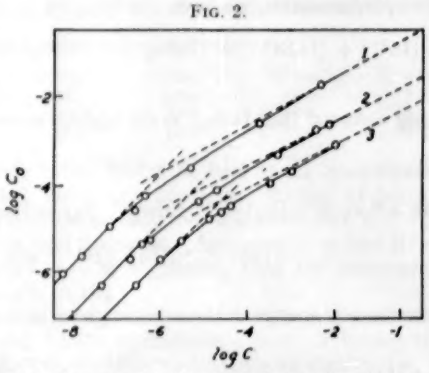

FIG. 1. *Dependence of distribution ratio upon total indium concentration for hydrobromic acid–isobutyl methyl ketone systems.*

Initial concns. of hydrobromic acid in the aqueous phase are 1·0, 0·6, 0·4, and 0·2N for curves 1, 2, 3, and 4 respectively. The ionic strength was made up to 1·0M with potassium nitrate for curves 2, 3, and 4.

FIG. 2. *Indium concentrations in isobutyl methyl ketone as a function of that in the aqueous phase.*

Initial concns. of hydrobromic acid in the aqueous phase are 1·0, 0·4, and 0·2N for curves 1, 2, and 3 respectively. No salt background was used in these equilibrations.

It has been shown that the value of the derivative $(\partial \log q/\partial \log [In^{3+}])_{[HBr]} = \bar{m} - \bar{m}$, where $\bar{m}$ is the average number of atoms of indium per molecule for all species in the organic phase and $\bar{m}$ is the corresponding ligand number for the aqueous phase (Part I). It will only be zero when both phases contain only species in the same degree of association. Under such conditions the derivative $(\partial \log q/\partial \log C_{In})_{[HBr]}$ should also be zero, and since this is found to be the case for indium concentrations less than $\sim 10^{-5}$M, it is reasonable to assume that all species are mononuclear there (cf. Part III). The negative value of the derivative at higher metal concentrations may then be taken as indicating a greater degree of association in the aqueous phase than in the organic phase. The experimental value of $-0{\cdot}5$ lies within the range, $0 \geqslant (\partial \log q/\partial \log [In])_{[HBr]} \geqslant -1$, which may be predicted where mononuclear and binuclear species coexist in the aqueous phase while only monomeric species are extracted. Were effectively the whole of the indium in the aqueous phase present as dimerised species, $C_o/\sqrt{C}$ would be constant so that

$$\log C_o = 0{\cdot}5 \log C + \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

while if all species are monomeric in the aqueous phase

$$\log C_o = \log C + \log q \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

Plots of log C_o against log C (Fig. 2) have unit slope at low metal concentrations, but the slope tends towards the value 0·5 at high concentrations suggesting that dimerisation is considerable in 0·1M-indium solutions. The nature of the dimerised species does not emerge from this oversimplified treatment, but if only one dimerised species predominated in the aqueous phase its probable composition can be deduced by the following treatment. First, it is desirable to consider whether the dimer might be a basic species containing, or bridged by, a hydroxyl group—especially as a similar type of phenomenon in the system zirconium–trifluorothenoylacetone-benzene has been interpreted by Connick and Reas (*J. Amer. Chem. Soc.*, **1951**, **73**, 1171) as arising from the hydrolysis and polymerisation of zirconium. However, at metal concentrations less than 10^{-5}M we may estimate the ratio of concentrations of the first bromide-ion complex, $InBr^{++}$, to that of the first hydrolysis product, $InOH^{++}$, in solutions of hydrobromic acid of strengths 0·2—1·0N as of the order of 10^4—10^6 (cf. Part III). Consequently, the possibility that the dimer is a hydroxylated species at higher metal concentrations may be considered remote. Later we advance more decisive evidence. Assuming for the moment that one indium–bromide dimeric species predominates, we have:

$$C = [In^{3+}] + [InBr^{++}] + [InBr_2^{+}] + [InBr_3] + [InBr_4^{-}] + [HInBr_4] + 2[In_2Br_r^{6-r}] \quad . \quad (3)$$

it being assumed that $InBr_4^-$ is the highest mononuclear complex present. Thence

$$C = a[In^{3+}] + b[In^{3+}](1 + K^{H}[H^{+}]) + 2\beta_{2,r}[In^{3+}]^2[Br^{-}]^r \quad . \quad . \quad . \quad (4)$$

where $K^{H} = [HInBr_4]/[H^+][InBr_4^-]$, $\beta_{2,r} = [In_2Br_r^{6-r}]/[In^{3+}]^2[Br^-]^r$,

$$\beta_n = [InBr_n^{3-n}]/[In^{3+}][Br^-]^n,\ a = \sum_{n=0}^{n=3} \beta_n[Br^-]^n, \text{ and } b = \beta_4[Br^-]^4 \quad . \quad . \quad (5)$$

If now the sole species in the organic phase is the acido-complex, $HInBr_4$,

$$C_o = [HInBr_4]_o = p_4K^{H}b[H^+][In^{3+}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $p_4 = [HInBr_4]_o/[HInBr_4]$. Substituting in equation (1) these values of C_o and C given by equations (4) and (6), and rearranging, we have

$$\frac{1}{q} = \frac{C}{C_o} = \frac{a + b(1 + K^{H}[H^+])}{p_4K^{H}b[H^+]} + \frac{2\beta_{2,r}[Br^-]^r\, C_o}{(p_4K^{H}b[H^+])^2} \quad . \quad . \quad . \quad . \quad (7)$$

If $1/q^o = \underset{C_o \to 0}{\text{Lim.}}\ (1/q)$, rearrangement of equation (7) gives

$$\frac{1}{2C_o}\left(\frac{1}{q} - \frac{1}{q^o}\right) = \frac{\beta_{2,r}[Br^-]^r}{(p_4K^{H}b[H^+])^2} = j \text{ (say)} \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Similarly, if indium tribromide were the only species in the organic phase,

$$C_o = p_3\beta_3[In^{3+}][Br^-]^3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6a)$$

where $p_3 = [InBr_3]_o/[InBr_3]$, and from equations (1), (4), and (6*a*)

$$j = \frac{1}{2C_o}\left(\frac{1}{q} - \frac{1}{q^o}\right) = \frac{\beta_{2,r}[Br^-]^{r-6}}{(p_3\beta_3)^2} \quad . \quad . \quad . \quad . \quad . \quad . \quad (8a)$$

Since j can readily be calculated from experimental data, its variation with $[Br^-]$ and $[H^+]$ according to equation (8) or (8*a*) will permit a decision as to the probable nature of the dimeric species in the aqueous phase—provided the composition of the extracted species is known. For this purpose we note that so long as the total concentration of indium is very much less than the concentrations of hydrobromic acid under consideration, $[H^+]$ =

$[Br^-] = C_{HBr}$. Introducing into equation (8) the value of b from equation (5), and substituting C_{HBr} for $[H^+]$ and $[Br^-]$, we have

$$j(C_{HBr})^{10-r} = \beta_{2,r}/(p_4 K^H \beta_4)^2 = \text{constant} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

for the case where $HInBr_4$ is extracted. Similarly from equation (8*a*), we have

$$j(C_{HBr})^{6-r} = \beta_{2,r}/(p_3\beta_3)^2 = \text{constant} \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

for the case where $InBr_3$ is extracted. It will be apparent from the method of derivation that if the dinuclear species contains hydrogen in addition to bromine atoms (*i.e.*, if it has the composition $In_2Br_{t+s}H_s^{6-t}$) equations of exactly the same form will result, provided only that the index r is now taken to represent the total number of ligands (hydrogen and bromide ions) associated with each pair of indium ions, *i.e.*, provided $r = t + 2s$.

Experimental values of q^o, and values of j calculated by successive approximation which enable values of q calculated from equations (8) or (8*a*) to fit the experimental data most closely, were obtained from the measurements in 0·2, 0·39, and 0·975M-hydrobromic acid. From Table 5 it is clear that values of $j(C_{HBr})^4$ are almost the same for the three

TABLE 5. *Determination of the value of the index, r.*

C_{HBr}, M	q^o	j	jC_{HBr}	$j(C_{HBr})^2$	$j(C_{HBr})^3$	$j(C_{HBr})^4$	$j(C_{HBr})^5$
0·20	2·18	8000	1600	320	64·0	12·8	2·6
0·39	12·7	600	234	91·2	35·6	13·9	5·4
0·975	180	15	14·6	14·3	13·9	13·5	13·2

acid concentrations. Analyses of the organic phase at the highest metal concentrations used gave consistent values for $HInBr_4$ (cf. Table 4). Moreover, studies of partition equilibria at tracer concentrations (Part III) indicate that this acido-complex is the predominant species extracted from hydrobromic acid solutions. Assuming then that $HInBr_4$ is the sole extractable species, we have $10 - r = 4$, suggesting that the predominant dinuclear species formed in the aqueous phase is In_2Br_6.

Systems with a Neutral Salt Background.—Although the ionic strength was constant in each series of experiments in 0·2, 0·39, and 0·975M-hydrobromic acid, it varied from one series to another. In order to examine the possible significance of this factor, the dependence of distribution ratio upon total metal concentration was remeasured for different concentrations of hydrobromic acid with a salt background of potassium nitrate to maintain an ionic strength of 1·0M throughout. It has been shown (Part III, *loc. cit.*) that indium nitrate does not pass by partition into *iso*butyl methyl ketone under these conditions, and that competitive complex-formation between bromide and nitrate ions is negligible.

The results (Fig. 1, curves 2, 3, and 4) for equilibrium acidities of 0·2, 0·375, and 0·563M-hydrobromic acid show the same general trend as those discussed above. Below indium concentrations of $\sim 10^{-5}$M, q is again constant; but it decreases at higher concentrations. Plots of log C_o against log C are found to have unit slope at low metal concentrations, and again the slope tends towards the value 0·5 at high metal concentrations. Comparison of measurements at similar acidities shows that the distribution ratios are lower in the presence of potassium nitrate. Whatever the origin of this salt effect may be, data obtained in the same medium are self-consistent, and since the possibility of competitive complex-formation had been eliminated, values of j were calculated as before. From Table 6 it appears that values of $j(C_{HBr})^3$ are most nearly

TABLE 6. *Determination of the index, r, in the presence of potassium nitrate at* $\mu = 1{\cdot}0$M.

C_{HBr}, M	q^o	j	jC_{HBr}	$j(C_{HBr})^2$	$j(C_{HBr})^3$	$j(C_{HBr})^4$
0·20	0·218	4000	800	160	32	6·4
0·375	1·72	581	2·18	82	30·8	11·5
0·563	7·63	160	90	50·7	28·6	16·1

constant, implying that the predominant dimeric species in the aqueous phase is $In_2Br_7^-$ in the presence of potassium nitrate as a background salt. As the method of calculation of the index r is based upon the simplifying assumptions that a single species, $HInBr_4$,

predominates in the organic phase and that polymerisation in the aqueous phase is confined to a predominant dinuclear species $In_2Br_r^{6-r}$, the discrepancy between the values of r found in the two media is not unreasonable.

The hypothesis being accepted that the decrease in distribution ratio of indium between hydrobromic acid and *iso*butyl methyl ketone at metal concentrations above 10^{-5}M is due to the formation of species such as In_2Br_6 and $In_2Br_7^-$ of low or negligible extractability when compared with that of the acido-complex $HInBr_4$, it is possible to estimate their stability. Irrespective of the salt medium and the precise value of β_4 which is assumed, the value of the product $p_4K^{II}\beta_4$ is found to be of the order 5×10^5 to 9×10^5 (cf. Part III). Hence, from equation (9) the equilibrium constant $\beta_{2,6}$ has the value 3×10^{12}—10^{13}. This leads to a value for the dimerisation constant of the reaction $2InBr_3 \rightleftharpoons In_2Br_6$ of the order of $\beta_{2,6}/(\beta_3)^2 = 5 \times 10^5$ to 4×10^6. Similarly, $\beta_{2,7} \sim 10^{13}$, and the equilibrium constant for the reaction $InBr_3 + InBr_4^- \rightleftharpoons In_2Br_7^-$ is $\beta_{2,7}/\beta_3\beta_4 \approx 10^7$.

We can now reconsider the possibility of the predominant dinuclear complex in the aqueous phase being a hydroxylated species, such as $In_2(OH)_q$. Corresponding to equation (3) we have

$$C = [In^{3+}] + [InBr^{++}] + \ldots . [InBr_4^-] + [HInBr_4] + 2[In_2(OH)_q] \quad . \quad (10)$$

Treating equation (10) in the same manner as equation (3), we find for the case where only the acido-complex, $HInBr_4$, is extracted into the organic phase

$$j(C_{HBr})^{10+q} = \beta_{2,q}K_w^q/(p_4K^{II}\beta_4)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $\beta_{2,q} = [In_2(OH)_q]/[In^{3+}]^2[OH^-]^q$, and K_w is the ion-product of water. Since from the experimental data summarised in Tables 5 and 6, the products $j(C_{HBr})^4$ and $j(C_{HBr})^3$ give the best agreement, we have $10 + q = 4$ or 3, whence $q = -6$ or -7. These are physically meaningless solutions which effectively dispose of the hypothesis that the dimer is a hydroxylated species.

Discussion.—Studies of partition equilibria at tracer concentrations of indium (Part III) and the macro-scale analyses now reported all indicate that the predominant species extracted from hydrobromic acid into *iso*butyl methyl ketone, diethyl ether, and many other solvents is the acido-complex $HInBr_4$. Analysis of the extracts in diethyl ether show that this species is associated with ten molecules of water. This degree of hydration does not appear unreasonable when comparison is made with the composition of the organic extract in other systems (cf. Table 7), although the very high hydration numbers reported in extraction by alcohols probably arise through some special hydroxyl

TABLE 7.

Species in organic phase	Solvent	Ref.
$HFeCl_4.4{\cdot}5H_2O$	2 : 2′-Dichlorodiethyl ether	*a*
$HFeCl_4.5H_2O$	Di*iso*propyl ether	*b*, *c*
$Al(NO_3)_3.9H_2O$	*n*-Hexanol	*d*
$UO_2(NO_3)_2.4H_2O$	Diethyl ether and other solvents	*e*
$Co(ClO_4)_2.14{\cdot}7H_2O$	Octan-2-ol	*f*
$Ni(ClO_4)_2.10H_2O$	Octan-2-ol	*f*

[a] Axelrod and Swift, *J. Amer. Chem. Soc.*, 1940, **62**, 33. [b] Nachtrieb and Conway, *ibid.*, 1948, **70**, 3547. [c] Campbell, A.E.C.U., 2313. [d] Templeton, *J. Phys. Coll. Chem.*, 1950, **54**, 1255. [e] McKay and Mathieson, *Trans. Faraday Soc.*, 1951, **47**, 428. [f] Yates, Laran, Williams, and Moore, *J. Amer. Chem. Soc.*, 1953, **75**, 2212.

mechanism; *initial* hydration numbers are often negative with alcohols. Preliminary experiments have shown that an ethereal extract containing $HInBr_4$ conducts electricity; so too does an ethereal solution of the similarly constituted salt NH_4GaCl_4 (Friedman and Taube, *J. Amer. Chem. Soc.*, 1950, **72**, 3362). Detailed experiments by Campbell (*loc. cit.*) show that $HFeCl_4.5H_2O$ behaves as a strong electrolyte when dissolved in *iso*propyl ether. The Raman spectrum of extracts from acid solutions of indium bromide into diethyl ether and *iso*butyl methyl ketone (Woodward and Bill, *J.*, 1955, 1699) proves to be that of the tetrahedral $InBr_4^-$ ion and provides further evidence of ionisation. Now the unsolvated molecule of $HInBr_4$ has a somewhat improbable electronic structure, and if the hydrated

complex, $HInBr_4$,aq., crosses the phase boundary, it probably does so in the form of the ion-pair $H_3O^+(H_2O)_nInBr_4^-$. In diethyl ether, $n = 9$; but it may have other values in different solvents.

Variations in distribution with total metal concentration may be interpreted in a number of ways. It may be postulated that activity coefficients are varying, that the presence of the extracted species has changed the solvent properties of the organic phase, or that changes in phase miscibility have altered the nature of both phases. For these, and for other reasons, stoicheiometric partition coefficients and stability constants may vary. At present it appears to be almost impossible to give quantitative expression to such hypotheses except for systems in which step-equilibrium may be neglected (Glueckauf, McKay, and Mathieson, *Trans. Faraday Soc.*, 1951, **47**, 437). The hydrobromic acid–*iso*butyl methyl ketone system was selected for detailed study after a survey of the partition of indium halides into a large number of solvents (Part V; *loc. cit.*) because variations in phase miscibility were negligible. From this it was inferred that changes in the solvent composition were negligible in both phases, so that the constancy of stoicheiometric partition coefficients and stability constants could be assumed. Activity coefficients have been controlled in the aqueous phase, and logical deductions made from the application of the law of mass action to the equilibria.

The hypothesis that the decrease in the distribution ratio of indium between hydrobromic acid and *iso*butyl methyl ketone at metal concentrations above 10^{-5}M is due to the formation of stable species such as In_2Br_6 and $In_2Br_7^-$ in the aqueous phase is supported by a growing body of evidence for the existence of polynuclear inorganic complexes in solution, and it is apparent that these occur more commonly than was formerly supposed. Thus dimeric halide species of the type M_2X_6 are well known in the vapour phase for indium (Brode, *Ann. Physik*, 1940, **37**, 344; Stevenson and Schomaker, *J. Amer. Chem. Soc.*, 1942, **64**, 2514) and for other tervalent metals, and have been demonstrated in solutions of iron and aluminium halides in non-associating organic solvents (Gmelin, " Handbuch der anorganische Chemie," Berlin, 1924). The addition of hydrobromic acid to a solution of Al_2Br_6 in benzene is known to give rise to the complex ion $Al_2Br_7^-$ (Dallinga, reported by van Eck, in Venanzi and Gamlen, *Chimia e l'Industria*, 1953, **35**, 926; cf. Brown and Pearsall, *J. Amer. Chem. Soc.*, 1952, **74**, 191). Although there is as yet less published information concerning dinuclear species in aqueous solution their presence has been established in mixtures of silver and chloride or bromide ions (Berne and Leden, *Svensk Kem. Tidskr.*, 1953, **65**, 88; *Z. Naturforsch.*, 1953, **11**, 719) and iodide or thiocyanate ions (Leden, personal communication). It is certain that the hydrolysis products of many ter- and quadri-valent aquo-cations, including indium, are extensively polymerised (Sillén, *Acta Chem. Scand.*, 1954, **8**, 299, 318; Mattock, *ibid.*, p. 777). The presence of polynuclear species in indium sulphate solutions has been reported by Sundén (*Svensk Kem. Tidskr.*, 1954, **66**, 20, 50) and may be inferred from his potentiometric data for other indium complexes. They have not been observed in measurements of the stability constants of indium halides with ion-exchange resins (Carleson and Irving, *J.*, 1954, 4390; Schufle and Eiland, *J. Amer. Chem. Soc.*, 1954, **76**, 960), doubtless owing to the low and small range of indium concentrations employed. Finally, the existence of dinuclear complexes of metals in different valency states bridged by hydroxyl or halide ions has been clearly established by studies of the kinetics of electron-transfer reactions (Amphlett, *Quart. Rev.*, 1954, **8**, 219, and refs. therein).

There is less evidence as to the stability of polynuclear complexes, though the values $[Fe_2(OH)_2^{4+}]/[Fe^{3+}]^2[OH^-]^2 \sim 10^{25}$ and $[Fe_2(OH)_2^{4+}]/[Fe(OH)^{2+}]^2 \sim 10^3$ (Hedström, *Arkiv Kemi*, 1953, **6**, 1) are suggestive. Independent confirmation of the existence and stability of indium–bromide ion complexes is clearly desirable and may be obtained potentiometrically.

Although the distribution ratio for indium between hydrobromic acid and *iso*butyl methyl ketone decreases with increasing metal concentration, yet with diethyl ether as solvent it increases, a result which is explicable if the degree of association in the organic phase is greater than in the aqueous phase. A similar situation obtains in the extraction of iron and gallium (Irvine, personal communication; cf. Dodson, Forney, and Swift,

J. Amer. Chem. Soc., 1936, **58**, 2573; Axelrod and Swift, *ibid.*, 1940, **62**, 33). With increasing metal concentration, extraction into 2 : 2′-dichlorodiethyl ether decreases, but into di*iso*propyl ether it increases. Such phenomena could be explained on the *ad hoc* hypothesis that dimeric species are extracted more readily than monomeric species into the aliphatic ethers, but considerably less readily into such solvents as *iso*butyl methyl ketone and chloro-ethers. If such were the case the extent of polymerisation of the extracted species should differ at different metal concentrations and also in the different classes of solvent. No such evidence has been advanced, however; on the contrary the absorption spectrum of the ferric chloride complex extracted into *iso*propyl ether obeys Beer's law over the range 10^{-2}—10^{-1}M (Nachtrieb and Conway, *ibid.*, 1948, **70**, 3547; Metzler and Myers, *ibid.*, 1950, **72**, 3776), and the extracts from indium bromide–hydrobromic acid mixtures into *iso*butyl methyl ketone and into diethyl ether have the same Raman spectra (Woodward and Bill, *loc. cit.*) and analytical composition (cf. Table 4). The apparent paradox could be explained if only monomeric species undergo partition, for their electrostatic association as ion-pairs, triplets, or even larger clusters will be favoured by solvents of very low dielectric constant (cf. Fuoss and Kraus, *ibid.*, 1933, **55**, 21) and would be greater in aliphatic ethers than in *iso*butyl methyl ketone or the chloro-ethers which have considerably larger dielectric constants. The effective degree of polymerisation of the metal in the aqueous phase may then become less than that prevailing in the organic phases composed of the former solvents, the difference increasing with the total metal concentration.

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THE INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD. [*Received, November 2nd*, 1954.]

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*The Extraction of the Indium Halides into Organic Solvents.**

By H. IRVING and F. J. C. ROSSOTTI.

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The extraction of indium at tracer concentrations from solutions in hydrochloric, hydrobromic, and hydriodic acid into ten organic solvents has been studied as a function of the concentration of halogen acid. Extraction into fifteen other solvents has been examined in less detail. The predominant species extracted is the hydrated acido-complex, $HInX_4$.aq. (X = Cl, Br, or I). In any one solvent the halides are extracted in the order iodide > bromide > chloride. For all three solutes, the effectiveness of those solvents studied in detail falls in the order methyl propyl (or *iso*propyl) ketone > *iso*butyl methyl ketone > furfuraldehyde > ethyl acetate > diethyl ether > *iso*pentyl alcohol > *iso*pentyl acetate > 2 : 2′-dichlorodiethyl ether > di*iso*propyl ether. These phenomena, and the partition equilibria are discussed in terms of the general treatment of the solvent extraction of inorganic solutes proposed in Part I.

IN a recent study of the solvent extraction of the halides of group IIIB metals (Irving and Rossotti, *Analyst*, 1952, **77**, 801) it was shown that, while indium may be almost quantitatively extracted by diethyl ether from hydrobromic acid or hydriodic acid, not more than 2·5% is extractable from hydrochloric acid if the phase volumes are initially the same. This work has now been extended to a detailed study of the extraction of indium from the three halogen acids with the object of ascertaining the relative efficiencies of extraction of different solvents for each halide in turn, of measuring the extent to which the relative extractabilities of the three indium halides vary from solvent to solvent, and of

* Part V of a group of papers of which Parts I—IV are the preceding papers.

correlating the new results with previous observations on the solvent extraction of other types of inorganic salts.

Several workers have reported on the extraction of indium halides by diethyl ether (Ato, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1934, **24**, 162; Wada and Ishii, *ibid.*, p. 135; Kitahara, *Reports Sci. Res. Inst. (Japan)*, 1948, **24**, p. 454; Bock, Kusche, and Bock, *Z. analyt. Chem.*, 1953, **138**, 167; Irving and Rossotti, *loc. cit.*). The extraction of indium from hydrobromic acid into *iso*propyl ether and from hydrochloric acid containing potassium iodide into ethyl acetate (Hudgens and Nelson, *Analyt. Chem.*, 1952, **24**, 1472), has been used analytically. Knox and Spinks (*Canad. Chem. Processing Ind.*, 1946, **30**, No. 11, 85) have reported on the extraction of concentrated solutions of indium in 6N-hydrochloric acid into a variety of organic solvents, and detailed studies have recently been made of the solvent extraction of indium from hydrobromic acid into *iso*butyl methyl ketone (Parts III and IV). The concentrations of indium employed in these investigations have ranged from 10^{-6}M to 6M; in some cases the extraction has not been studied over a range of acid concentrations, in others it is impossible to calculate values for distribution coefficients and for the acidities of the aqueous phases at equilibrium from the incomplete published data. Detailed comparison of results is thus frequently impossible.

In the present work the solvents studied in detail were chosen from commercially available ketones, aldehydes, esters, alcohols, and ethers. They were methyl propyl, methyl *iso*propyl, and *iso*butyl methyl ketone, furfuraldehyde, ethyl acetate, *iso*pentyl acetate, *iso*pentyl alcohol, and diethyl, di*iso*propyl, and 2 : 2′-dichlorodiethyl ether. A few experiments were made with *n*-butaldehyde, *cyclo*hexanone, nitromethane, nitrobenzene, and benzonitrile, all of which appeared to extract indium efficiently from its solutions in halogen acids. Hydrocarbons and chlorinated hydrocarbons were not investigated in such detail, but their ability to extract indium was consistently extremely low and generally negligible. Solvents of that type examined included benzene, toluene, xylene, *n*-hexane, *cyclo*hexane, chloroform, carbon tetrachloride, dichloroethane, and chlorobenzene. Carbon disulphide also appeared to be incapable of extracting indium.

For each system the initial and final acidities of the aqueous phase, N' and N, the initial and final volume of the aqueous phase, V' and V, and the initial and final volume of the organic phase, V_o' and V_o, were measured. The percentage of indium extracted, and the distribution ratio, q, were determined radiometrically with ^{114}In as tracer. In all the present experiments the volumes of the aqueous and the organic phases before equilibration were made equal ($V_o' = V'$), and neither phase was pre-saturated with the other. Here and elsewhere, the subscript, o, is used to distinguish quantities referring to the organic phase from those referring to the aqueous phase. The prime (*e.g.*, in V') is used to distinguish the values of phase volumes, acidities, counting rates, etc., before equilibration from the corresponding values after equilibration; this reverses the less satisfactory convention adopted in Part III.

The initial concentration of acid, N', was varied until it approached a value at which the phases became completely miscible. Owing to the large range of acidities thus investigated it was impossible to maintain the ionic strength of the aqueous phase at a constant value. Ideally, a complete study would include measurements of distribution ratios in which the concentration of indium is varied widely for each system; but here the concentrations of indium were maintained in the region of 10^{-5}M throughout. The effects of changes in metal concentration and in other variables have been investigated in detail for the system hydrobromic acid–*iso*butyl methyl ketone and are reported elsewhere (Parts III and IV). To assist in interpreting the results, the effect of changes in the concentration of halogen acids in the aqueous phase upon the solubility of water in certain of the organic phases was studied.

Values of the distribution ratio, q, and the percentage extraction, E, were calculated from the expressions:

$$q = C_o/C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$E = 100V_oC_o/(V_oC_o + VC)$$
$$= 100qR/(1 + qR) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where C_o, C refer to the total concentration of indium in any form in the organic and the aqueous phase, respectively, after equilibration, and $R = V_o/V$ is the ratio of the phase volumes after equilibration. Care was taken that all measurements referred only to systems at equilibrium. The rate of attainment of equilibrium was followed by observing the rate of increase (or decrease) of radioactivity in the organic (or aqueous) phase respectively, or in the apparent change in distribution ratio with the time of shaking. Under the experimental conditions finally adopted (below), 2—3 min. proved sufficient for the attainment of equilibrium and a standard time of shaking of 5 min. was adopted throughout. Such a short period is in agreement with previous observations on the extraction of other inorganic salts (cf. Nachtrieb and Conway, *J. Amer. Chem. Soc.*, 1948, **70**, 3547; Wylie, *J.*, 1951, 1474) but is in striking contrast with the long periods of equilibration needed for the solvent extraction of metals as inner complexes with, *e.g.*, oxine, cupferron, and dithizone (Dyrssen, *Svensk Kem. Tidskr.*, 1953, **65**, 43; Irving, Bell, and Williams, *J.*, 1952, 356).

Experimental

Materials.—Radioactive ^{114}In (half-life 49 days) was obtained by irradiation of "Specpure" indium wire of known weight for periods up to two months at the Atomic Energy Research Establishment, Harwell, at a flux of 8×10^{11} neutrons cm.$^{-2}$ sec.$^{-1}$. A stock solution of concentration $3{\cdot}4 \times 10^{-3}$M in N-sulphuric acid was obtained by dissolving the irradiated metal in hot 6N-sulphuric acid. For extraction experiments the stock solution was diluted to give solutions of a convenient level of activity.

Ethers were tested for the absence of peroxides, and purified if necessary by standard methods (Weissberger and Proskauer, "Organic Solvents," Oxford, 1935). Catechol (50 mg./l.) was added to the *iso*propyl ether as a stabilising agent and the stocks were kept in the dark. Peroxidation of 2 : 2′-dichlorodiethyl ether was so rapid that purification and distillation was necessary immediately before use. Furfuraldehyde was redistilled and stabilised with catechol. The remaining solvents were of a good laboratory grade and were redistilled before use.

Hydriodic acid was redistilled over red phosphorus in an atmosphere of nitrogen within a day of use and stored in the dark. Good laboratory grades of hydrochloric acid, and of bromine-free hydrobromic acid were available.

General Procedure.—In the distribution experiments neither phase was presaturated with the other. Indium solutions of the desired concentration in halogen acid (20 ml.) and organic solvent (20 ml.) were introduced into a 60-ml. Pyrex glass test-tube fitted with a carefully ground-in B24 stopper. Equilibration was effected by mechanical shaking in a horizontal position for 5 min. at 150 cycles per minute. The tubes were then placed vertically and the phases allowed to separate completely at room temperature (13° ± 3°). This was rapid in most systems, but occasionally some minutes and even hours were necessary for complete separation (cf. p. 1963). The levels of the menisci were marked on vertical paper strips affixed to the outsides of the tubes. After the tubes had been emptied, washed, and thoroughly dried, water was run in from a burette up to the marks and the values of the phase volumes after equilibration, V_o and V, were so obtained. The standard deviation of such measurements was found to be 0·5—1·0%. Aliquot portions of each phase were removed in calibrated pipettes for analysis, great care being taken to avoid any contamination of one phase by the other.

Indium analyses were made by radio-assay of ^{114}In using 20th Century Electronics G.M.6 liquid counters. For the comparatively volatile solvents such as diethyl and di*iso*propyl ether and ethyl acetate, the oxine precipitation method described previously (Irving and Rossotti, *Analyst*, 1952, **77**, 801) was employed. With the other solvents aliquots of the initial and the equilibrated aqueous phases only were analysed and the activity in the organic phase was obtained by difference. Under comparable conditions of counting, $C' : C : C_o = Z' : Z : Z_o$, where Z is the counting rate corrected for paralysis time and background. As the radioactive indium was assayed in a standard solution no self-absorption corrections were necessary in the oxine procedure. Correction for decay of the comparatively long-lived ^{114}In was also unnecessary provided aliquot portions for any one experiment were assayed consecutively. The duration of counting was always sufficient to give a standard deviation of 1% or less. For mass balance, $V'C' = VC + V_oC_o$, thus permitting a check on experimental procedures (Irving and

Rossotti, *loc. cit.*). Equilibrium acidities were determined by dilution of aliquots and titration with 0·1N-sodium hydroxide.

Attainment of Equilibrium.—This was confirmed for any one solvent by shaking a number of identical samples of organic and aqueous phase for various times. Typical results are shown below. As equilibration was always attained in the order of 2—3 min., a shaking time of 5 min. was considered adequate and adopted throughout.

Extraction of indium by diethyl ether from 2N-*sulphuric acid containing* 0·1M-*potassium iodide.*

Time (min.)	0·5	1·0	1·5	2·0	5·0	10·0
Z (counts per min.)	8,142	11,267	11,500	12,484	12,484	12,494

Results of Partition Experiments.—In the following Tables N′, N are the normalities of the aqueous phase before and after equilibration, V and V_o the volumes of the aqueous and organic phases after equilibration, and q and E the distribution ratio and the percentage of indium extracted into the organic phase as defined by equations (1) and (2). Before equilibration the aqueous and organic phases were of equal volume, $V_o' = V' = 20$ ml. Each solvent is designated by a Roman numeral to facilitate reference to later Tables.

Determination of the Water Content of the Organic Phase.—The dependence of the equilibrium concentration of water in the organic phase upon the concentration of halogen acid in the aqueous phase was determined for systems involving hydrochloric (and hydrobromic) acid and diethyl ether, di*iso*propyl ether, ethyl acetate, *iso*pentyl acetate, and *iso*pentyl alcohol. Aliquot parts of the organic phase, after equilibration, were analysed for water by the Karl Fischer method (*Angew. Chem.*, 1935, **48**, 394). The titration apparatus described by Bonner (*Analyst*, 1946, **71**, 483) was constructuted by Mr. A. Jenkins. Minor modifications included provision for magnetic stirring and a siphon for the removal of solutions, after titration, under pressure of dry nitrogen. The automatic burettes and reservoirs were fitted with guard tubes of magnesium perchlorate, and the nitrogen was dried by passage through a tower of silica gel. Platinum

II. *Methyl propyl ketone.*

(a) 5·14 × 10^{-4}M-*Indium in* HCl.

N′	N	V_o	V	E	q
0·20	0·186	18·5	21·5	0	0
0·375	0·36	18·9	21·1	7·2	0·0869
0·75	0·70	19·1	20·9	20·6	0·284
1·0	0·95	18·8	21·2	35·4	0·618
1·5	1·40	18·45	21·55	61·9	1·894
2·0	1·84	18·25	21·75	78·9	4·46
3·0	2·74	18·1	21·9	93·5	17·5
4·0	3·50	17·6	21·4	97·3	44·3
6·0	3·86	9·25	30·75	96·0	80·0

(b) 5·14 × 10^{-5}M-*Indium in* HBr.

0·025	0·024	18·9	21·1	2·3	0·0263
0·05	0·048	18·85	21·15	12·3	0·158
0·10	0·095	18·9	21·1	45·0	0·915
0·20	0·190	18·9	21·1	83·2	5·53
0·40	0·379	18·9	21·1	97·0	36·2
1·00	0·92	18·2	21·8	99·8	516
3·50	2·52	14·3	25·7	99·9	1121
4·00	Completely miscible				

(c) 5·14 × 10^{-5}M-*Indium in* HI.

0·0025	—	18·9	21·1	1·7	0·0188
0·0050	—	18·7	21·3	11·9	0·1535
0·010	—	18·7	21·3	60·1	1·716
0·015	—	18·65	21·3	86·0	7·02
0·020	—	18·9	21·1	93·6	16·3
0·025	—	18·9	21·1	97·75	48·6
0·050	—	18·7	21·3	99·7	377·5
2·0	1·375	19·4	20·6	99·7	386
2·5	Completely miscible				

III. *Methyl* iso*propyl ketone.*

(a) 5·14 × 10^{-5}M-*Indium in* HCl.

0·10	0·092	18·3	21·7	0	0
0·25	0·24	18·45	21·55	1·8	0·0214
0·50	0·455	18·4	21·6	7·3	0·0925
0·75	0·71	18·7	21·3	23·0	0·340
1·00	0·91	18·5	21·5	38·1	0·716
1·50	1·38	18·3	21·7	64·1	2·12
2·00	1·81	17·9	21·15	79·6	4·84
3·00	2·70	17·7	22·3	93·9	19·5
4·00	3·38	16·4	23·7	97·3	51·9
6·60	3·78	8·3	31·8	97·1	127·7

(b) 5·14 × 10^{-5}M-*Indium in* HBr.

0·02	—	18·4	21·6	0	0
0·03	—	18·4	21·6	3·6	0·044
0·05	—	18·2	21·8	12·2	0·166
0·10	0·093	18·5	21·5	49·5	1·14
0·20	0·186	18·6	21·5	86·0	7·07
0·375	0·350	18·4	21·6	96·8	35·6
1·00	0·90	17·9	22·1	99·8	535
3·00	2·41	15·0	25·0	99·9	1362
4·00	2·16	2·95	37·0	63·4	21·7

(c) 5·14 × 10^{-5}M-*Indium in* HI.

0·0025	—	18·45	21·55	0	0
0·0050	—	18·3	21·7	6·8	0·0864
0·010	—	18·4	21·6	45·5	0·982
0·015	—	18·4	21·6	71·1	2·89
0·020	—	18·3	21·7	86·7	7·74
0·025	—	18·35	21·65	89·9	10·5
0·050	—	18·2	21·8	99·4	202·2
2·50	2·10	16·25	23·75	99·2	186·5

IV. *isoButyl methyl ketone.*

(a) 5·14 × 10^{-6}M-*Indium in* HCl.

n′	n	V_o	V	E	q
0·105	0·10	20·0	20·0	1·1	0·0113
0·51	0·50	20·3	20·1	4·8	0·0495
1·00	0·976	19·65	20·4	6·8	0·0755
1·50	1·45	20·15	20·3	32·2	0·478
2·04	2·00	19·5	20·65	53·2	1·204
3·00	2·94	20·15	20·15	79·3	3·82
4·00	3·87	19·5	20·8	91·1	10·84
5·00	4·71	19·9	20·8	94·3	19·37
7·00	6·38	18·3	22·15	96·7	36·0
8·00	6·40	15·9	24·2	97·1	51·0

(b) 5·14 × 10^{-6}M-*Indium in* HBr.

0·050	0·050	20·0	20·0	3·7	0·0386
0·10	0·10	20·0	20·0	10·0	0·111
0·20	0·20	20·0	20·0	49·9	0·995
0·40	0·40	20·0	20·0	86·4	6·34
0·50	0·50	20·0	20·0	92·9	13·1
0·75	0·73	19·5	20·5	97·8	47·4
1·00	0·975	19·5	20·5	99·1	119
3·00	2·89	19·1	20·9	99·8	459
6·00	4·63	23·6	16·7	99·2	89·1

(c) 1·72 × 10^{-6}M-*Indium in* HI.

0·005	—	19·9	20·1	3·9	0·0406
0·010	—	19·7	20·3	36·1	0·582
0·015	—	19·6	20·4	57·0	1·38
0·020	—	19·8	20·2	72·6	2·70
0·050	0·0498	19·8	20·2	99·0	97·6
0·10	0·10	19·8	20·2	99·7	325
0·15	0·135	19·6	20·4	99·9	1215
0·50	0·49	19·5	20·5	99·9	1190
4·00	3·18	24·8	15·2	99·7	213·5

V. *Furfuraldehyde.*

(a) 7·92 × 10^{-6}M-*Indium in* HCl.

0·10	0·098	19·5	20·4	2·9	0·031
1·00	0·97	19·3	20·5	9·1	0·106
2·00	1·87	18·6	21·3	21·6	0·315
3·00	2·76	18·2	21·7	42·4	0·879
3·76	3·20	16·8	23·2	58·2	1·925
4·86	3·80	14·0	25·6	64·1	3·27
5·66	3·40	6·85	33·15	41·0	3·37

(b) 7·92 × 10^{-6}M-*Indium in* HBr.

0·10	0·0975	19·4	20·5	2·8	0·0304
0·25	0·20	19·45	20·55	20·1	0·266
0·50	0·44	18·8	20·7	37·0	0·648
0·80	0·72	18·8	20·8	61·0	1·73
1·00	0·96	18·8	20·8	77·4	3·79
1·53	1·28	18·2	21·55	89·6	10·2
1·98	1·79	18·15	21·75	96·6	33·6
2·50	2·04	16·8	22·9	97·8	60·2
3·32	2·05	11·85	28·0	91·2	24·5

(c) 7·92 × 10^{-6}M-*Indium in* HI.

0·016	—	19·7	20·2	5·1	0·0548
0·034	—	19·75	20·15	20·0	0·255
0·040	—	19·6	20·1	30·1	0·442
0·060	—	19·65	20·05	63·8	1·80
0·106	0·100	19·6	20·0	92·7	12·9
0·250	0·247	19·4	20·2	99·3	138·6
0·495	0·490	19·35	20·2	~100	1000
1·98	1·95	19·7	20·2	97·1	34·5

VI. *Ethyl acetate.*

(a) 3·30 × 10^{-6}M-*Indium in* HCl.

0·99	0·95 *	18·95	21·05	0·3	0·0034
1·60	1·51	19·0	21·2	1·0	0·00986
2·00	1·88	18·7	21·3	1·8	0·0203
2·13	1·96	18·3	21·8	1·8	0·0214
3·00	2·76	18·4	21·75	5·1	0·0638
4·00	3·56	17·5	22·5	11·7	0·170
4·90	4·20	16·7	23·3	21·4	0·379
5·79	4·52	13·45	26·65	33·4	0·995
7·00	4·02	5·2	34·8	25·7	2·32

(b) 3·30 × 10^{-6}M-*Indium in* HBr.

0·016	0·10 *	18·7	21·3	0·6	0·00631
0·263	0·25	19·1	21·1	4·7	0·0548
0·50	0·467	18·4	21·8	14·8	0·206
1·00	0·92	18·6	21·6	61·3	1·84
1·99	1·79	17·85	22·15	95·2	24·4
3·08	2·61	16·5	23·6	99·3	198
4·02	3·10	13·85	25·95	98·6	136
4·50	2·80	9·25	30·75	92·2	39·2
5·05	2·68	1·6	37·7	32·8	11·5

(c) 3·30 × 10^{-6}M-*Indium in* HCl.

0·017	0·016 *	19·0	21·05	0	0
0·031	0·029	19·0	21·05	0·4	0·00434
0·054	0·051	19·0	20·95	29·2	0·454
0·11	0·10	18·85	21·15	78·8	4·17
0·25	0·23	18·5	21·6	98·3	67·5
0·48	0·45	18·5	21·5	99·8	588
1·91	1·57	15·7	24·2	~100	1828
2·44	1·74	12·0	28·05	97·5	90·7
2·75	1·56	5·0	35·15	52·8	7·87

VII. *Diethyl ether.*

(a) 2·64 × 10^{-4}M-*Indium in* HCl.

4·00	3·46	16·5	22·6	0·7	0·00095
5·00	4·05	15·6	23·7	1·4	0·022
6·00	4·70	13·2	25·5	2·6	0·05

(b) 1·03 × 10^{-4}M-*Indium in* HBr.

0·50	0·465	18·0	21·6	2·0	0·024
1·00	0·91	18·0	22·0	9·6	0·129
2·00	1·80	17·4	22·5	51·6	1·375
3·00	2·58	16·35	23·3	89·3	11·9
4·00	3·26	15·1	24·4	96·5	44·2
5·00	3·43	10·0	29·2	70·9	7·1

(c) 5·4 × 10^{-4}M-*Indium in* HI.

0·10	0·09	17·85	21·95	39·4	0·80
0·25	0·22	17·85	21·8	93·3	17·1
0·49	0·44	17·1	22·6	99·4	211·0
1·55	1·27	16·6	23·2	99·9	1033
2·05	1·60	14·4	25·35	99·3	246
2·50	1·87	12·2	27·4	96·1	54·8
3·15	1·92	6·3	32·8	48·6	4·92
3·50	1·97	6·0	33·2	37·9	3·37

VIII. iso*Pentyl alcohol.*

(a) 1·72 × 10^{-5}M-*Indium in* HCl.

N′	N	V_o	V	E	q
3·00	2·53	21·75	18·25	0	0
4·00	3·31	22·45	17·55	4·2	0·0345
5·00	4·00	23·45	16·55	8·7	0·0672
6·00	4·74	24·8	15·2	15·0	0·108
7·00	5·49	26·4	13·55	19·1	0·121
8·00	6·10	29·1	10·9	30·4	0·164
9·00	6·62	33·3	6·7	52·3	0·221

(b) 1·72 × 10^{-5}M-*Indium in* HBr.

0·50	0·375	20·7	19·3	0	0
1·00	0·724	20·9	19·1	2·4	0·0223
2·00	1·35	21·6	18·4	15·9	0·161
3·00	1·98	22·05	18·0	35·2	0·444
4·00	2·55	22·65	17·4	57·7	1·05
5·00	3·12	23·3	16·7	74·6	2·10
6·00	3·72	24·3	15·7	86·8	4·24
7·00	4·30	25·55	14·45	93·2	7·78
8·00	4·85	27·45	12·55	96·1	11·3
9·00	5·65	29·7	10·3	97·2	12·2

(c) 1·72 × 10^{-5}M-*Indium in* HI.

0·05	0·05	20·6	19·4	2·6	0·0254
0·10	0·095	20·6	19·4	26·3	0·336
0·15	0·135	20·7	19·3	40·9	0·644
0·20	0·17	20·6	19·4	65·0	1·75
0·40	0·325	20·8	19·2	93·1	12·5
0·50	0·425	20·8	19·2	96·2	23·2
1·00	0·74	21·4	18·6	99·2	109
2·00	1·46	22·5	17·5	99·5	155
3·00	2·17	23·4	16·6	99·4	116
4·38	3·20	25·6	14·45	99·4	91·2

X. 2 : 2′-*Dichlorodiethyl ether.*

(a) 5·14 × 10^{-5}M-*Indium in* HCl.

5·00	4·72	20·0	20·0	0·5	0·0047
6·00	5·72	20·0	20·0	5·6	0·596
7·00	6·62	20·0	20·0	10·1	0·112
8·00	7·57	20·0	20·0	16·7	0·200
9·00	8·44	20·0	20·0	20·6	0·260
10·0	9·23	20·0	20·0	19·5	0·242

(b) 5·14 × 10^{-5}M-*Indium in* HBr.

0·50	0·494	20·0	20·0	0·4	0·0037
1·00	0·99	20·0	20·0	7·0	0·0753
1·50	1·39	20·0	20·0	17·1	0·207
2·00	1·88	20·0	20·0	40·5	0·680
2·50	2·36	20·0	20·0	57·8	1·37
3·00	2·84	20·0	20·0	80·6	4·15
4·00 †	3·82	20·0	20·0	97·4	37·7
5·00 †	4·71	20·0	20·0	99·2	128
6·00 †	5·69	20·0	20·0	99·6	247

(c) 5·14 × 10^{-5}M-*Indium in* HI.

0·10	0·091	20·0	20·0	0	0
0·143	0·127	20·0	20·0	6·5	0·069
0·25	0·22	20·0	20·0	10·5	0·117
0·30	0·27	20·0	20·0	30·9	0·448
0·358	0·33	20·0	20·0	42·0	0·726
0·40	0·36	20·0	20·0	48·3	0·935
0·60	0·55	20·0	20·0	86·6	5·96
0·75	0·70	20·0	20·0	94·4	16·8
1·00	0·912	20·0	20·0	98·2	53·6
6·00 †	5·35	20·0	20·0	99·6	270

IX. iso*Pentyl acetate.*

(a) 4·29 × 10^{-5}M-*Indium in* HCl.

5·00	4·87 *	19·5	20·5	0·2	0·00157
5·95	5·70	19·4	20·6	0·8	0·00856
6·95	6·60	19·1	20·9	4·8	0·055
8·00	7·55	18·85	21·15	6·6	0·079
8·80	8·15	18·4	21·6	12·1	0·161
9·80	8·50	19·0	21·1	11·1	0·1378

(b) 1·72 × 10^{-5}M-*Indium in* HBr.

0·50	0·42 *	20·0	20·0	0	0
1·00	0·98	19·6	20·4	4·8	0·0529
1·50	1·47	19·5	20·5	15·0	0·186
2·00	1·96	19·5	20·4	37·7	0·630
2·50	2·45	19·55	20·45	76·4	2·38
3·00	2·94	19·5	20·5	85·8	6·35
4·00	3·94	19·47	20·53	97·6	42·3
5·00	4·88	19·5	20·5	99·4	167·8
7·10	6·69	19·6	20·4	99·75	414
7·80	7·20	22·4	17·6	99·75	318

(c) 1·72 × 10^{-5}M-*Indium in* HI.

0·030	0·030 *	20·0	20·0	2·5	0·0257
0·050	0·050	20·1	19·9	3·8	0·0386
0·100	0·100	20·1	19·9	14·4	0·166
0·200	0·196	19·55	20·45	56·3	1·35
0·250	0·240	19·6	20·4	74·9	3·10
0·500	0·490	19·6	20·4	97·2	36·7
0·750	0·735	19·7	20·3	99·4	164
5·00	4·54	21·7	18·3	99·9	843
6·00	5·38	29·0	11·0	99·9	468

XI. *Diisopropyl ether.*

(a) 2·06 × 10^{-5}M-*Indium in* HCl.

5·94	5·82	20·0	20·0	0·2	0·0016
7·95	7·25	18·15	21·55	0·85	0·0102
9·95	6·86	10·75	28·95	2·2	0·0602

(b) 1·17 × 10^{-5}M-*Indium in* HBr.

1·00	0·98	19·6	20·4	0·5	0·0056
2·00	1·95	19·55	20·45	4·8	0·053
3·12	2·94	19·55	20·45	36·1	0·592
4·00	3·65	19·2	20·8	79·8	4·28
5·00	4·80	19·2	20·8	95·0	20·4
6·00	5·56	18·45	21·55	99·0	119
6·72	5·60	15·95	24·0	76·8	4·97
7·80	5·50	7·9	31·1	7·0	0·297

(c) 2·06 × 10^{-5}M-*Indium in* HI.

0·252	0·236	20·0	20·0	19·9	0·249
0·510	0·510	20·0	20·0	71·9	2·56
0·750	0·713	19·45	20·55	95·4	21·8
1·01	0·973	19·25	20·7	99·3	142
2·00	1·96	19·6	20·4	100	2088
4·40	4·04	18·3	21·7	100	2775
4·94 ‡	4·20	14·35	22·25	34·9	18·5
		3·15	—	62·2	151
5·22 ‡	3·72	11·15	19·4	23·7	1·81
		9·45	—	53·7	4·85
5·32 ‡	3·08	9·5	25·4	14·2	0·52
		5·1	—	13·4	0·895
5·50	2·56	9·3	30·5	15·3	0·591

* These figures are for the final acidity of the halogen acid only and do not include acetic acid formed by hydrolysis.

† At these acidities the organic phase formed the upper layer.

‡ Double entries refer to "light" and "heavy" organic phases respectively.

N′	N	V	V	E	q
XII. *Butaldehyde.*					
(b) $7{\cdot}92 \times 10^{-5}$M-*Indium in* HBr.					
1·01	0·94	17·7	21·2	73·5	3·32
1·43	1·33	17·9	21·5	88·3	9·09
2·03	1·86	17·6	21·9	97·8	54·5

N′	N	V_0	V	E	q
XIII. cyclo*Hexanone.*					
(b) $5{\cdot}14 \times 10^{-5}$M-*Indium in* HBr.					
0·2	—	18·5	21·5	95·9	27·1

XIV. *Miscellaneous solvents.* The values given are for the distribution coefficient (q) between 4N-hydrobromic acid and the organic solvent named, 4×10^{-6}M-indium being used.

Solvent	q	Solvent	q
Benzene	0	CCl_4	0
Toluene	0·001	$(CH_2Cl)_2$	0·0055
Xylene	0·004	Chlorobenzene	0·001
n-Hexane	0	Nitromethane	27·5
*cyclo*Hexane	0	Nitrobenzene	51·5
CS_2	0	Benzonitrile	440
$CHCl_3$	0·003		

electrodes were connected to a Mullard potentiometer incorporating a cathode-ray tube, and the dead-stop end-point was used. Direct titration was adopted and the end-point was taken to be that for which the " magic-eye " remained open for an arbitrary length of time, *viz.*, 25 sec. (Mitchell and Smith, " Aquametry," Interscience Publ., New York, 1948).

Anhydrous methanol was prepared by refluxing it over magnesium foil and then distilling it (Weissberger and Proskauer, " Organic Solvents," Oxford, 1935). A standard solution of water was obtained by making up 5·0535 g. of distilled water to 1 l. with this anhydrous methanol. Karl Fischer reagent was supplied by Messrs. B.D.H. Ltd., and was of approximately equivalent strength.

After the Karl Fischer reagent had been standardised against the standard solution of water, a convenient aliquot portion (0·25—2·00 ml.) of the organic phase was discharged into the titration vessel from an accurately calibrated pipette against a counter current of nitrogen which was maintained during the titrations to ensure an inert atmosphere. Replicate analyses had a standard deviation of 1·3%. In the following Table [H_2O] is the concentration of water in moles per l. of organic phase and N′ is the initial normality of halogen acid. The volumes of organic solvent and halogen acid were equal before equilibration.

VI. *Ethyl acetate.*								
(*a*) HCl, N′	0·0	0·94	2·88	3·72	5·5	6·4		
[H_2O]	1·46	1·33	1·10	1·03	0·86	0·89		
(*b*) HBr, N′	0·0	0·98	1·87	2·66	3·58	4·45		
[H_2O]	1·46	1·36	1·28	1·18	1·12	1·20		
VII. *Diethyl ether.*								
(*a*) HCl, N′	0·0	0·94	1·89	2·88	3·72	4·61	5·54	7·77
[H_2O]	0·46	0·44	0·39	0·35	0·31	0·28	0·24	0·19
(*b*) HBr, N′	0·0	0·98	1·87	2·66	3·57	4·45	5·35	
[H_2O]	0·46	0·41	0·38	0·34	0·32	0·29	0·28	
VIII. iso*Pentyl alcohol.*								
(*a*) HCl, N′	0·0	1·90	3·72	5·54	7·58	8·93		
[H_2O]	4·5	5·16	7·34	10·4	14·8	19·5		
(*b*) HBr, N′	0·0	1·87	4·45	5·35	7·66			
[H_2O]	4·52	6·11	10·0	12·0	18·4			
IX. iso*Pentyl-acetate.*								
(*a*) HCl, N′	0·0	0·94	2·88	4·61	6·40	7·58	9·02	
[H_2O]	—	0·57	0·48	0·38	0·34	0·32	0·58	
(*b*) HBr, N′	0·0	0·98	2·66	4·45	5·35	6·02	7·66	
[H_2O]	0·61	0·57	0·48	0·44	0·54	0·78	7·15	
XI. *Diisopropyl ether.*								
(*a*) HCl, N′	0·0	0·94	2·88	4·61	7·58			
[H_2O]	0·208	0·196	0·170	0·140	0·101			
(*b*) HBr, N′	0·0	0·98	1·87	3·57	5·37	7·66		
[H_2O]	0·208	0·201	0·188	0·148	0·124	0·109		

Discussion

Comparison with Previous Work.—Ato's results (*loc. cit.*) for 10^{-2}M-indium in the ether–hydrochloric acid system agree satisfactorily with ours so far as direct comparison is possible. There is also good agreement with the data of Hudgens and Nelson (*loc. cit.*) who

worked with indium concentrations down to 10^{-3}M in the *iso*propyl ether–hydrobromic acid system. Detailed comparison with Wada and Ishii's results (*loc. cit.*) for the extraction of $4{\cdot}4 \times 10^{-2}$M-indium into diethyl ether is not possible as the Japanese workers do not record values for distribution ratios or equilibrium acidities, but the present results suggest that at low acidities the extraction of indium is more effective at the concentration level of $\sim 10^{-5}$M we have employed. However the values obtained in the present work are consistently lower than those reported by Bock, Kusche, and Bock (*loc. cit.*) who used 10^{-1}M-indium, and the amount of indium extracted from hydrobromic acid into ether appears to increase with indium concentration (cf. Part IV).

The effect of changes in acidity on the distribution of indium halides is conveniently displayed by plotting the logarithm of the distribution ratio, q, against the logarithm of the acidity, N, of the aqueous phase after equilibration. For extraction from hydriodic acid, all the solvents studied gave curves of a similar form (Fig. 1). Log q first increases almost linearly with log [HI], then passes through a fairly sharp maximum, and finally falls off more or less rapidly.

Families of similar curves for extraction from hydrobromic acid are shown in Fig. 2. Those representing extraction from hydrochloric acid (Fig. 3) have rather steeper slopes than those shown in Figs. 1 and 2, particularly for extraction into the " less efficient " solvents, *i.e.*, solvents which effect appreciable extraction only at high acidities.

Form of Distribution Curves.—A complete discussion, in quantitative terms, of the distribution for all the systems investigated is impossible, partly because the ionic strength in the aqueous phase was not constant (see p. 1947) and partly because increasing miscibility of the phases with increasing acidity entails many complications. But, provided that the concentration of indium in the system is small compared to that of all other species (as in the experiments under consideration), its distribution should not materially affect that of any other species which undergo partition, *e.g.* water, organic solvent, or halogen acid; the value of the distribution coefficient should, in turn, be determined essentially by the composition of the organic and the aqueous phase. Neglecting for the moment the effect of any changes in phase compositions on the partition coefficients and stability constants of the various species present in equilibrium, the dependence of q on the concentration variables in the aqueous phase follows from the general treatment proposed in Part I. At the low indium concentrations ($\sim 10^{-5}$M) used in the present work it can reasonably be assumed that no polynuclear species are present in the aqueous or the organic phases (cf. Parts III and IV), and the average composition of the complex species in the organic and aqueous phases may be represented by $\mathrm{H}_{\bar{\mathbf{h}}}\mathrm{InX}_{\bar{\mathbf{n}}}$ and $\mathrm{H}_{\bar{h}}\mathrm{InX}_{\bar{n}}$ respectively, where X = Cl, Br, or I, and $\bar{h}$ and $\bar{n}$ are " ligand numbers " giving the average number of hydrogen or halide ions respectively attached to each atom of indium. Ligand numbers referring to the organic phase are distinguished by heavy (Clarendon) type from those referring to the aqueous phase which are in italics.

Equation (I) may now be written

$$q = [\mathrm{H}_{\bar{\mathbf{h}}}\mathrm{In\ X}_{\bar{\mathbf{n}}}]_{\mathbf{0}}/[\mathrm{H}_{\bar{h}}\mathrm{InX}_{\bar{n}}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and, introducing definitions for (stoicheiometric) partition coefficients and stability constants, *viz.*,

$$p_{\bar{h}1n} = [\mathrm{H}_{\bar{h}}\mathrm{InX}_{n}]_{\mathbf{0}}/[\mathrm{H}_{\bar{h}}\mathrm{InX}_{n}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\beta_{\bar{h}1n} = [\mathrm{H}_{\bar{h}}\mathrm{InX}_{n}]/[\mathrm{H}^{+}]^{\bar{h}}[\mathrm{In}^{3+}][\mathrm{X}^{-}]^{n} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

we obtain

$$\log q = \log p_{\bar{\mathbf{h}}1\bar{\mathbf{n}}}\,\beta_{\bar{\mathbf{h}}1\bar{\mathbf{n}}}/\beta_{\bar{h}1\bar{n}} + (\bar{\mathbf{h}} - \bar{h}) \log [\mathrm{H}^{+}] + (\bar{\mathbf{n}} - \bar{n}) \log [\mathrm{X}^{-}] \quad . \quad (5)$$

In this treatment (cf. Part I) it is assumed that the degree of solvation and hydration does not change over the range of acid and halide-ion concentrations studied, and that activity coefficients are constant.

In a solution where the strong halogen acid HX is the only source of hydrogen and

FIG. 1.

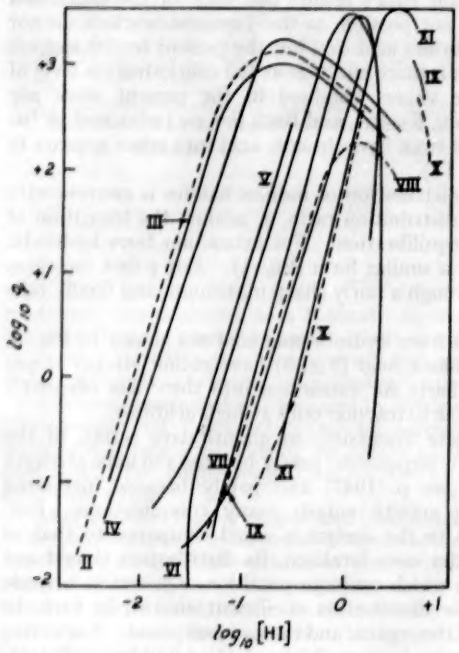


FIG. 2

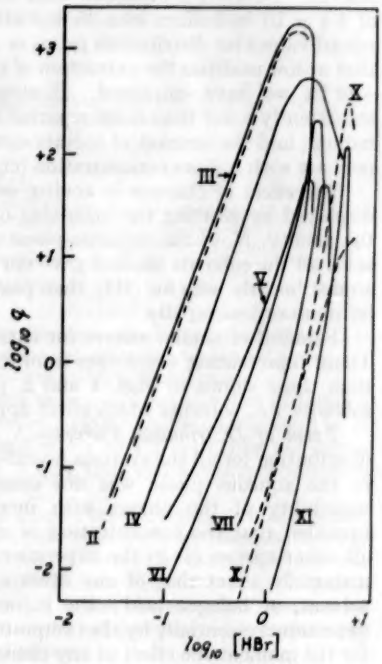
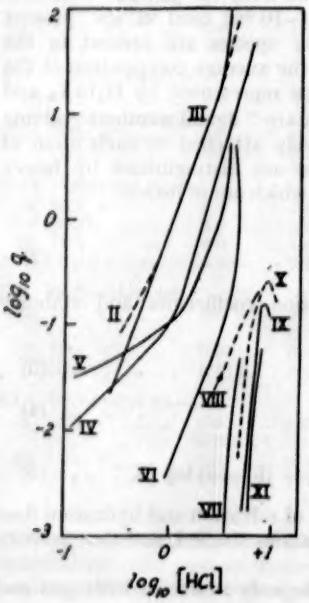


FIG. 3.



The extraction of indium from (FIG. 1) *hydriodic acid,* (FIG. 2) *hydrobromic acid,* (FIG. 3) *hydrochloric acid. The variation of distribution ratios with equilibrium acidities.*

halide ions, and where its concentration C_{HX} is greatly in excess of the total concentration C_{In} of indium we have $[H^+] = [X^-] = C_{HX}$, so that equation (5) reduces to:

$$\log q = \text{constant} + \{(\bar{h} - \bar{h}) + (\bar{n} - \bar{n})\}\log C_{HX}$$

and

$$(\partial \log q/\partial \log C_{HX}) = (\bar{h} - \bar{h}) + (\bar{n} - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad (6)$$

There is no evidence for higher halide complexes than InX_4^- in aqueous solutions (Carleson and Irving, *J.*, 1954, 4390, and refs. therein) so that the maximum value of $\bar{n}$ is 4 in these equations.

If InX_3 were the sole metallic species in the organic phase, then

$$\underset{C_{HX} \to 0}{\text{Lim.}} \quad (\partial \log q/\partial \log C_{HX}) = 3$$

and

$$\underset{C_{HX} \to \infty}{\text{Lim.}} \quad (\partial \log q/\partial \log C_{HX}) = -2$$

and at moderate acidities

$$(\partial \log q/\partial \log C_{HX}) = (3 - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

if the reasonable assumption be made that $\bar{h} \approx 0$. At present there is no evidence that metal acido-complexes are not strong acids (cf. for ferrocyanic acid, Nekrassov and Zotov, *J. Appl. Chem. U.S.S.R.*, 1941, **14**, 264; *Chem. Abs.*, 1942, **36**, 1834). Similarly, if $HInX_4$ were the sole species in the organic phase, then

$$\underset{C_{HX} \to 0}{\text{Lim.}} \quad (\partial \log q/\partial \log C_{HX}) = 5; \quad \underset{C_{HX} \to \infty}{\text{Lim.}} \quad (\partial \log q/\partial \log C_{HX}) = 0$$

and at moderate acidities

$$(\partial \log q/\partial \log C_{HX}) = (5 - \bar{n}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

For a given halogen acid, HX, at any arbitrary concentration C_{HX}, $[X^-]$ is fixed (provided $C_{HX} \gg C_{In}$) so that $\bar{n}$ (which is a function only of $[X^-]$ and the various stability constants, β) is also fixed. Hence the gradient of all curves of log q against log C_{HX} should be the same for a given value of C_{HX}. But since $\bar{n}$ increases with C_{HX}, the slope should decrease as the acid concentration is increased and we should expect for different solvents a family of curves, convex towards the concentration axis and differing only by a vertical displacement corresponding to changes in the values of log p_{hln} for the different solvents. Consider finally the case where InX_3 and $HInX_4$ undergo partition simultaneously. At low values of C_{HX} where the degree of complex formation in the indium–halide ion system is low, InX_3 will predominate in the organic phase, irrespective of the relative magnitudes of the partition coefficients p_{013} and p_{114}. Thus the gradient $\partial \log q/\partial \log C_{HX}$ approaches the value 3 as C_{HX} approaches zero; but since the amount of the complex InX_4^- formed increases in proportion to $[X^-]^4$, while that of InX_3 increases only in proportion to $[X^-]^3$, $\partial \log q/\partial \log C_{HX}$ will tend to the value $(5 - \bar{n})$ as C_{HX} increases. If, however, $p_{114} \gg p_{013}$ (*i.e.*, the partition coefficient for the acido-complex $HInX_4$ is much larger than that of the neutral species InX_3), $\partial \log q/\partial \log C_{HX}$ will approximate to $(5 - \bar{n})$ for all values of C_{HX}. If, on the contrary, $p_{114} \ll p_{013}$, $\partial \log q/\partial \log C_{HX}$ will approximate to $(3 - \bar{n})$ at low values of C_{HX} (where $\bar{n}$ is also low), but to $(5 - \bar{n})$ at high values of C_{HX} (where the value of $\bar{n}$ will also be larger). Changes in the gradient of the plot of log q against log C_{HX} will therefore be less than would have been the case had either InX_3 or $HInX_4$ been the sole species extracted; indeed the graph may appear to be effectively linear over a limited concentration range (cf. Figs. 1, 2, and 3), or even concave to the concentration axis.

The Experimentally Determined Distribution Curves.—In the main, all the experimental results may be interpreted on the basis of the foregoing discussion though the phenomena are clearly more complex with hydrochloric acid than with the other halogen acids. The

discussion will be limited in the first instance to positive values of $\partial \log q/\partial \log C_{HX}$. For the iodide system (Fig. 1) the slope of plots of log q against log C_{HI} approximate to 4 for all solvents studied; for the bromide system (Fig. 2) the slopes of plots of log q against log C_{HBr} approximate to 3 for all solvents. For each acid, the similar value of the slope at corresponding acidities supports the hypothesis that the same type of predominating species is extracted irrespective of the solvent. The gradient of 4 found for the iodide system excludes the possibility that InI_3 is the predominant species in the organic phase [cf. equation (7)], and points towards $HInI_4$. Indeed a detailed analysis of the system indium bromide–hydrobromic acid–*iso*butyl methyl ketone (Parts III and IV) establishes that the predominant species extracted from acid solutions is $HInBr_4$,aq. If it is assumed that an acido-complex $HInX_4$ is the predominant species extracted from hydriodic or hydrobromic acid by all solvents, then the mean value of $\bar{n}$ is of the order of 1 and 2 respectively in the concentration regions studied [cf. equation (8)]. It is apparent from the known stability constants of indium halide ion complexes (Carleson and Irving, *loc. cit.*) that the iodide ion complexes are less stable than those with bromide ions and these values for $\bar{n}$ appear quite reasonable (cf. Part IV).

At macro-concentrations of indium it has been shown by analysis that $HInCl_4$ is the predominant species extracted from hydrochloric acid into *iso*butyl methyl ketone (Irving and Rossotti, unpublished observation). $HInBr_4$,aq. is known to be extracted from hydrobromic acid into diethyl ether or *iso*butyl methyl ketone (Part IV). The presence of the $InBr_4^-$ ion in such organic extracts is supported by a study of their Raman spectra (Woodward and Bill, unpublished work). Indeed there is a wealth of data pointing to the predominant extraction of acido-complexes, HMX_4,aq., into aliphatic ethers from acid solutions of tervalent halides at macro-concentrations, *e.g.*, for Fe^{3+} (Axelrod and Swift, *J. Amer. Chem. Soc.*, **1940**, **62**, **33**; Nachtrieb and Fryxell, *ibid.*, **1948**, **70**, **3552**; Bock, Kusche, and Bock, *loc. cit.*), for Au^{3+} (Mylius, *Z. anorg. Chem.*, 1911, **70**, **203**; Bock, Kusche, and Bock, *loc. cit.*; Haas, Ph.D. Thesis, Chicago, 1950), for Ga^{3+} (Nachtrieb and Fryxell, *J. Amer. Chem. Soc.*, **1949**, **71**, **4035**; Bock, Kusche, and Bock, *loc. cit.*), and for In^{3+} and Tl^{3+} (Bock, Kusche, and Bock, *loc. cit.*). There is also evidence that non-acidic species, MX_3, will partition in certain circumstances (Part III, and refs. therein), but at macro-concentrations the assumption that the acido-complex, $HInX_4$,aq., is the predominant species extractable from halogen acids may be considered established.

Individual distribution curves (Figs. 1, 2, and 3) are surprisingly linear in those portions where the gradient $\partial \log q/\partial \log C_{HX}$ is positive. It has been pointed out (p. 1955) that the co-extraction of InX_3 with $HInX_4$ provides a mechanism for counteracting the predicted convexity of such distribution curves towards the concentration axis. Another factor is that the dependence of phase miscibility on C_{HX} (p. 1964) limits variations in this term to little more than one logarithmic unit even in favourable cases and curvature of the distribution curves may not become apparent over so limited a range.

On changing from one solvent to another into which extraction occurs less readily it is necessary to proceed to higher acidities (and consequently to higher values of $\bar{n}$) to achieve a given value of q. Hence a somewhat lower value of the gradient [$= (5 - \bar{n})$ by equation (8)] would be expected in such solvents; the reverse behaviour is generally found. Moreover, slopes greater than 5 are found in extractions from hydrochloric acid, especially with the less efficient solvents with which very high acidities (4N to 9N) are required to yield appreciable extraction. Such high slopes cannot be explained in terms of the simplified theory put forward above (cf. Part I) and it is evident that a number of complicating factors must be considered.

In deriving equation (5) it was postulated that concentrations could be used in place of activities; in the present experiments it was impossible to control the ionic strength. The activity coefficients of the halogen acids increase very markedly with concentration (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950) and a partial correction may be applied by plotting log q against the logarithm of the activity of the acid used. A more serious difficulty in applying equation (5) to the results of the present experiments is that it refers strictly to what we have termed "ideal" extraction systems (Part I), *i.e.*, those in which the nature and

composition of the phases does not change with changes in acid concentration so that (stoicheiometric) partition coefficients and stability constants may be considered truly constant over the whole range of experimental conditions. This will certainly not be valid for solvents whose miscibility with water is strongly dependent on acid concentration (p. 1964), and equation (5) will then become less applicable as the acid concentration is increased, irrespective of the solvent, and still less applicable for the less efficient solvents. As the aqueous phase becomes increasingly organic in character as complete miscibility is approached, stability constants and the extent of the formation of extractable species are likely to increase. But if the dissociation of hydrogen and halide ions also increases appreciably, competition of indium and of hydrogen ions for halide ions will tend to lower $\bar{n}$.

In deducing equation (5) it was further assumed that the extent of solvation of the extracted species does not vary with acid concentration, and that the activity of water and of organic solvent in the two phases is likewise constant. Although this condition may be met when tracer concentrations of metal are used and a solvent is chosen whose miscibility with the aqueous phase does not change with acid concentration (Part IV), conditions are certainly more complex in many of the present experiments. It is known that $HInBr_4$ is accompanied by 10 molecules of water when extracted into diethyl ether (Part IV); if this water is closely associated with the complex the tenth power of the activity of the water should enter into the equilibrium conditions. But as the concentration of hydrogen halide in the aqueous phase is increased, the activity of water there is decreased, some water is transported into the organic phase by the acido-complex as it undergoes partition, and organic solvent passes into the aqueous phase. For such reasons no simple treatment of distribution at high acidities, or into highly miscible solvents, can be expected.

Retrograde Extraction.—The distribution curves for the indium halides frequently exhibit maxima (Figs. 1, 2, and 3), and at sufficiently high acidities the values of the gradient, $\partial \log q/\partial \log C_{HX}$, become negative. If the species which undergoes partition is the highest complex formed in the aqueous phase, its partition coefficient is given by the limiting value of the distribution ratio, q, as the free ligand concentration is indefinitely increased (Part I), and many examples are afforded by the extraction of inner complexes of metals with organic reagents (cf. Dyrssen, *Svensk Kem. Tidskr.*, **1953**, **65**, **43**; Dyrssen and Dahlberg, *Acta Chem. Scand.*, **1953**, **7**, 1186). In the absence of changes in phase composition, negative values of $\partial \log q/\partial \log C_{HX}$ then indicate the formation of higher complexes in the aqueous phase than that which undergoes partition (Part I). Thus in the system ferric thiocyanate–diethyl ether, the occurrence of a maximum value of q was correlated with a maximum in the fraction of iron present as the extractable species $Fe(CNS)_3$, higher anionic species being formed increasingly at higher concentrations of thiocyanate ion (Macdonald, Mitchell, and Mitchell, *J.*, 1951, 1574). However, with indium systems there is no evidence for higher complexes than InX_4^- in aqueous solutions (Carleson and Irving, *loc. cit.*). Moreover the negative values of the gradient are extremely large and even approach infinity, so that the decrease in extraction at high acidities requires some explanation other than a shift in the step-equilibria towards higher complexes than that extracted.

It appears that decreases in distribution coefficient always coincide with gross changes in phase volumes on equilibration in the present experiments. Data for the extraction of gallium, indium, and thallium halides into diethyl ether (Irving and Rossotti, *loc. cit.*) indicate that the retrograde extraction observed with these metals into any one of the halogen acids takes place at the same acidity and is independent of the nature of the metal. The phenomenon is thus specific for each acid–solvent combination and may be correlated with the rapid decrease in partition coefficients with approaching complete phase miscibility (Part I). Metzler and Myers (*J. Amer. Chem. Soc.*, **1950**, **72**, **3776**) correlated the maximum in the extraction of ferric chloride from hydrochloric acid into ethers with the miscibility of aqueous and organic phases in these systems.

Curves of Percentage Extraction.—For all the solvents studied in detail the percentage of indium extracted increases at first with the increasing initial concentration of acid, N', in the aqueous phase. Such increases in E are due, in the first instance, to increases in the

distribution ratio, q, which in turn can be related to the increasing formation in the aqueous phase of the particular species which undergoes partition (cf. equation 13 of Part I). At higher acidities the percentage extraction, defined by equation (2), usually passes through a maximum and eventually decreases. The percentage of indium extracted

FIG. 4.

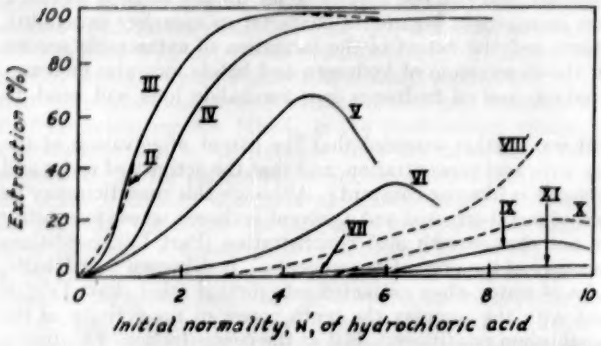
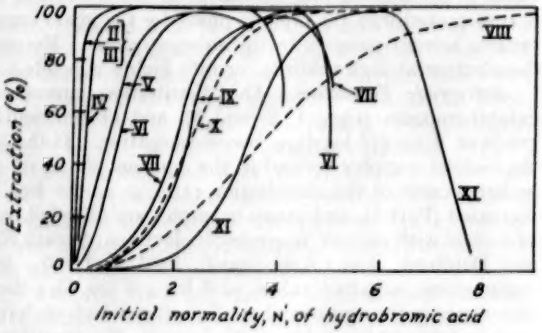
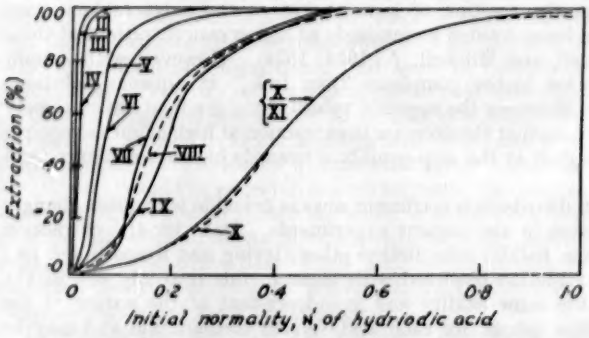


FIG. 5.



The percentage of indium extracted from (FIG. 4) *hydrochloric acid,* (FIG. 5) *hydrobromic acid,* (FIG. 6) *hydriodic acid by an equal volume of organic solvent.*

FIG. 6.



from hydrochloric acid is shown in Fig. 4. Even from the best solvents (methyl propyl and methyl *iso*propyl ketone), quantitative extraction is not attained until acid of initial normality 5N is used, while with the less efficient solvents (2 : 2′-dichlorodiethyl and di*iso*-propyl ether) the maximum extraction of a few percent is not attained until acid of strength ~9N is used. The corresponding curves for extraction from hydrobromic acid (Fig. 5) are generally similar but the maximum extraction occurs at appreciably lower initial acidities

(1—6N). In extractions from hydriodic acid (Fig. 6; note the greatly expanded scale of initial normalities) this trend is further accentuated and maximum extraction is achieved with all solvents below $N' = 1$, and for the most efficient solvents at an initial concentration of no more than 0·1N-hydriodic acid. In all these extractions, both the distribution ratio, q, and the ratio of phase volumes at equilibrium, R, depend on the acidity at equilibrium, N. Hence the sign of the gradient $\partial E/\partial N$ will depend upon the signs and relative magnitudes of both $\partial R/\partial N$ and $\partial q/\partial N$, and the present results illustrate the wide variety of behaviour which may be expected in different systems. With *iso*pentyl alcohol, E increases monotonically with acidity for each halogen acid because there is a concomitant increase in R and an increase in q with increasing acidity. The situation is analogous to the extraction of nitrates into diethyl ether from nitric acid where V_e also increases at the expense of V on equilibration, and where no retrograde extraction is observed. In the extraction of indium from hydrochloric acid by ethyl acetate or by furfuraldehyde the decrease in R soon outweighs the increase in q, and E passes through its maximum value at

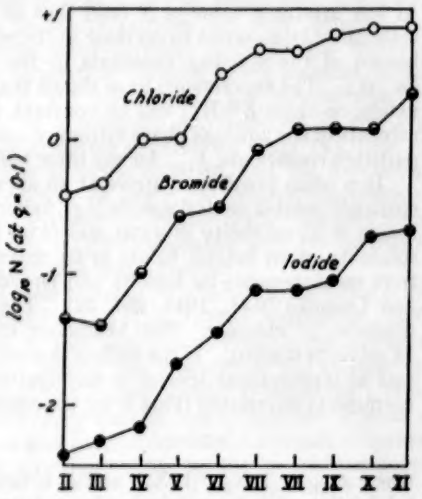


FIG. 7. *The order of solvent efficiency.* (*The organic solvents denoted by Roman numerals are named in Table 2.*)

less than 100% extraction. In these two systems q may still be capable of further increase although the acidity of the aqueous phase after equilibration has reached the largest value realisable under the present experimental conditions. This is presumably because the nature of the phases is still being modified in a manner favourable to partition. The converse behaviour, *viz.*, a sharp decrease in the value of q, will result when the phase compositions become less favourable to partition. The effect on the value of E will be greatest at high initial acidities where q is approaching a limiting value owing to the approaching identity of phases, and where the phase ratio, R, is large. In the *iso*pentyl alcohol–hydriodic acid system, q passes through a maximum (Fig. 1) even though the equilibrium acidity, N, is still increasing; however, as the rate of increase in R is comparatively small, the effect on E is scarcely perceptible at the highest acid concentrations examined.

The Order of Solvent Efficiency.—The concentration of halogen acid required in the aqueous phase to afford an arbitrary distribution of metal may be used as a measure of the relative efficiency of the different solvents. As an empirical basis for such comparisons values of log N corresponding to log $q = -1$ were read off from plots (Figs. 1, 2, and 3). This choice of $q = 0{\cdot}1$ was made to avoid long extrapolations, but the same conclusions could be drawn from values of log q corresponding to, *e.g.*, log $N = 0$. The values of log N are plotted as ordinates in Fig. 7, and the different solvents have been arranged in a monotonic series which holds, with but minor modifications, for each halogen acid. The

order of decreasing efficiency is methyl propyl or methyl *iso*propyl ketone > *iso*butyl methyl ketone > furfuradehyde > ethyl acetate > diethyl ether > *iso*pentyl alcohol > *iso*pentyl acetate > 2 : 2′-dichlorodiethyl ether > di*iso*propyl ether. For any one solvent the extraction efficiency decreases to much the same extent on replacement of hydriodic acid by hydrobromic acid, or of hydrobromic acid by hydrochloric acid. Assuming the predominant species extracted to be $HInX_4$,aq. in every case, we have (cf. Part I)

$$q = p_{114}\alpha_4 K^{II}[H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where p_{114} is the partition coefficient of the species $HInX_4$, $K^{II} = [HInX_4]/[H^+][InX_4^-]$ and α_4 is the degree of formation of the species InX_4^- in the aqueous phase. Here

$$\left.\begin{aligned} \alpha_n &= \beta_{01n}[X^-]^n / \sum_{n=0}^{n=4} \beta_{01n}[X^-]^n \\ \text{and} \quad \beta_{01n} &= [InX_n]/[In^{3+}][X^-]^n \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

At any arbitrary value of N (and thus at an arbitrary value of $[X^-]$ and $[H^+]$), α_4 may reasonably be assumed to decrease in the order chloride > bromide > iodide, from what is known of the stability constants in the indium–halide systems (Carleson and Irving, *loc. cit.*). The experiments have shown that q increases in the order chloride < bromide < iodide, so since $K^{II}[H^+]$ will be constant (unless the effects of small amounts of organic solvents in the aqueous phase introduce quite unexpected anomalies), the magnitude of the partition coefficients, p_{114}, for the three halide complexes will increase in the same order.

It is often possible to arrive at an approximate value for the partition coefficient of a sparingly soluble neutral species (*e.g.*, iodine, sulphur hexafluoride) by independent measurements of its solubility in water and in an organic solvent. Table 1 shows the ratio of the solubility of an indium halide in an organic solvent to its solubility in water, calculated from measurements by Ensolin and Dreyer (*Z. anorg. Chem.*, 1942, **249**, 119) and Ensolin and Lessman (*ibid.*, 1947, **254**, 92). These are seen to decrease in the order iodide > bromide > chloride. The behaviour of acetone is the sole exception amongst the 14 solvents studied. If the indium is assumed to exist as the trihalide in the organic phase and as mononuclear species in the aqueous phase, then distribution ratios and partition coefficients are related (Part I) by the equation

$$q = \alpha_3 p_{013} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $p_{013} = [InX_3]_o/[InX_3]$, and α_3 is defined by equation (10). From the known molar solubilities of indium trichloride, tribromide, and tri-iodide in water (5·73, 6·74, and 6·36 moles/l.; Ensolin and Dreyer, *loc. cit.*) and the known stability constants (Carleson and Irving, *loc. cit.*) values of α_3, the degree of formation of the trihalide complexes in the saturated aqueous solution, can be estimated as 0·75, 0·7, and 0·65 respectively, so that the magnitudes of the partition coefficients for InX_3 must increase in the order chloride < bromide < iodide.

TABLE 1. *The ratio of the solubilities of indium halides in various organic solvents to their solubilities in water (at 22°).*

Solvent	$InCl_3$	$InBr_3$	InI_3	Solvent	$InCl_3$	$InBr_3$	InI_3
Chloroform	0·023	0·039	0·97	Diethyl ether	0·523	0·887	0·921
Pentanol	0·344	0·612	0·640	Acetone	0·570	0·898	0·807
Pentyl acetate	0·393	0·697	0·795	Ethyl alcohol	0·59	0·69	—
Ethyl acetate	0·573	0·745	0·843				

Relation between the Efficiency of a Solvent as an Extracting Agent and its Physical Properties.—The energy needed to transfer a substance across a phase boundary may be regarded as arising from the greater stability of the (solvated) species in the organic phase compared with that in the aqueous phase (McKay, A.E.C.U. 2246). The existence of an order of solvents which alters very little with the nature of the material extracted would suggest that such stability factors depend more on the properties of the two phases than on the intrinsic nature of the solute.

The ten solvents investigated in detail and those other solvents which were found extract indium efficiently, *viz.*, butaldehyde, *cyclo*hexanone, nitromethane, and benzonitrile, are all electron donors, and it is of interest that the donor atom need not be oxygen. Previous workers on solvent extraction have adopted the viewpoint that the order of extractability by a series of solvents is that of their power to form hydrogen bonds (Katzin and Ferraro, *J. Amer. Chem. Soc.*, **1953**, **75**, 3821; Wylie, *J.*, **1951**, **1474**). The order of the strengths of hydrogen bonds formed between deuterated methanol and organic solvents is reported as alcohols > ethers > ketones > aldehydes > esters > nitro-compounds (Stanford and Gordy, *J. Chem. Phys.*, 1940, **8**, 170). For the particular solvents investigated in detail in this paper, their order is diethyl ether > di*iso*propyl ether > 2 : 2′-dichlorodiethyl ether and pentyl acetate > ethyl acetate > furfuraldehyde > *iso*butyl methyl ketone. Clearly the order of solvents now found experimentally cannot be explained in terms only of the Gordy index, $\Delta\nu$, of hydrogen-bond formation. Wiberley, Clark, and Bassett (U.S. Atomic Energy Commission Declassified Reports, New York Operations, 609), by using a spectroscopic technique similar to that of Gordy, found little correlation between the capacity of amines and ethers to accept protons and their behaviour as solvents, although it was clear that an electron donor–acceptor mechanism is involved. Gordy and Stanford (*loc. cit.*) observed little correlation between dipole moment, μ, and $\Delta\nu$. The former must be a relevant factor in the solvation of the species which is extracted and so in the extractive efficiency of a solvent. Acido-species of the type HMX_4,aq., probably exist as ion pairs and act as strong electrolytes (Part IV). An ion pair will be the more stable in a medium of low dielectric constant, but the free energy of transfer of the species undergoing partition will be lower the greater the dielectric constant of the organic phase. Solvents which extract water most readily are also found to extract inorganic salts most readily, and this may be correlated with the increasing dielectric constant of the organic phase with increasing water content.

It has frequently been observed that the lowest member of a homologous series is the most efficient extractant (Wylie, *loc. cit.*; Templeton and Hall, *J. Phys. Colloid Sci.*, **1947**, **51**, 1441; Warner, *Austral. J. Appl. Sci.*, **1952**, **3**, 156) and such an effect is substantiated by the present results. On steric grounds, the smaller the molecule of the solvent, the more readily should it be able to become attached to the species which is extracted. However the greater effectiveness of the lowest homologue may be due to any one or more of a number of causes, since almost any property which may be considered relevant to solvent extraction (cf. Table 2) generally has its most favourable value for the lowest homologue.

TABLE 2. *The solvents arranged in order of decreasing efficiency, and values of some of their physical constants.**

Number	Solvent	$\Delta\nu$	μ	ε	S	$10^3(MV)^{-1}$
II	Methyl propyl ketone	—	2·70	15·4	1·62	9·4
III	Methyl *iso*propyl ketone	—	2·76	—	1·94	9·4
IV	Methyl *iso*butyl ketone	77	2·79	13·1	1·25	7·8
V	Furfuraldehyde	70	3·57	42	3·22	12·0
VI	Ethyl acetate	84	1·82	6·02	1·5	10·2
VII	Diethyl ether	130	1·17	4·33	0·52	9·6
VIII	*iso*Pentyl alcohol	—	1·82	5·7	4·34	9·2
IX	*iso*Pentyl acetate	90	1·82	4·63	0·49	6·8
X	2 : 2′-Dichlorodiethyl ether	84	2·58	21·2	0·19	8·6
XI	Di*iso*propyl ether	123	1·2	3·88	0·25	7·1

* The frequency shift, $\Delta\nu$, is proportional to the strength of the hydrogen bond (Gordy and Stanford, *loc. cit.*). Values of μ refer to solutions in benzene at 20° (Wesson, "Tables of Electric Dipole Moments," Massachusetts Inst. Technology, 1948). The dielectric constants, ε, are taken from Maryott and Smith's "Tables of Dielectric Constants of Pure Liquids," Nat. Bur. Standards Circular 514, 1951. Molar solubilities, S, of water in the organic solvents, and reciprocal molar volumes $(MV)^{-1}$, at 20° are calculated from data in Mellan's "Industrial Solvents," Reinhold Publ. Corp., New York, 1950.

The substantially identical extraction efficiency of the metameric methyl propyl and methyl *iso*propyl ketones is not surprising as their physical properties are much the same, and the branched-chain isomer is unlikely to offer much greater steric hindrance to solvation.

Table 2 presents values for most of the physical properties which have been considered

relevant to discussions of solvent extraction. The solvents are arranged in order of decreasing efficiency for the extraction of indium halides (cf. Fig. 7). While detailed correlation is impossible, most of these physical properties have large values for the best extracting solvents. Conversely, the hydrocarbons, and the other less efficient solvents which were not studied in great detail, have low values of $\Delta\nu$ (where they have been measured), low values of ϵ, and low or zero values of μ and S.

General "orders of solvents" have been proposed by several workers in the field of chromatography (Trappe, *Biochem. Z.*, 1940, **305**, 150; Lacourt, Sommereyns, Geyndt, and Jacquet, *Mikrochem.*, 1951, **36**, 117; Lederer and Lederer, "Chromatography," Elsevier, London, 1953). While a completely general order cannot be expected (Part I) it is of interest to compare the present results with those for the extraction of other inorganic salts. In Table 3 the solvents used in the present work are again designated by Roman

TABLE 3. *The correlation of solvent orders.*

System	Ref.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
In–HCl	*a*	1	2	3	4	5	6	7	8	9	10	11
In–HBr	*a*	2	1	3	4	5	6	7	8	9	10	11
In–HI	*a*	1	2	3	4	5	6	7	8	9	10	11
In–HCl	*b*	1	—	—	3	2	—	4	—	5	—	—
Ga–HCl	*c*	—	4	—	1	—	3	2	5	6	7	8
Ga–HBr	*c*	—	1	—	2	—	5	3	6	—	—	4
Ga–HI	*c*	—	1	—	2	—	3	4	—	—	—	—
Fe–HCl	*d*	1	—	—	—	—	2	3	4	—	—	—
Fe–HCl	*e*	—	—	—	—	—	—	1	—	—	2	3
Fe–HBr	*f*	—	—	—	1	—	2	3	—	—	—	4
Au–HBr	*f*	—	—	—	1	—	2	3	—	—	—	4
Pb–HI	*g*	—	—	1	2	—	3	—	—	—	—	—
HNO_3	*h*	—	1	—	2	—	—	3	—	—	5	4
HNO_3	*i*	—	1	—	—	—	—	2	—	—	—	—
La^{3+}–HNO_3	*i*	—	1	—	4	—	2	6	3	5	—	—
Ce^{4+}–HNO_3	*i*	—	2	—	—	—	—	1	—	—	—	3
Th^{4+}–HNO_3	*i*	—	2	—	1	—	3	6	4	5	7	8
UO_2^{2+}–HNO_3	*j*	1	—	—	2	—	—	3	4	—	6	5
UO_2^{2+}–HNO_3	*h*	1	—	—	2	—	—	3	—	4	—	5
R.E.–HNO_3	*l*	—	—	—	—	—	3	2	1	4	—	—

a, Present work. *b*, Knox and Spinks, *loc. cit.* *c*, Milner, Wood, and Woodhead, A.E.R.E. C/R 1041. *d*, Kutznetsov, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 175. *e*, Axelrod and Swift, *J. Amer. Chem. Soc.*, 1940, **62**, 33; Nachtrieb and Fryxell, *ibid.*, 1948, **70**, 3552. *f*, McBryde and Yoe, *Analyt. Chem.*, 1948, **20**, 1094. *g*, West and Carlton, *Analyt. Chim. Acta*, 1952, **6**, 406. *h*, Wylie, *loc. cit.* *i*, Bock and Bock, *Z. anorg. Chem.*, 1950, **263**, 146. *j*, Warner, *loc. cit.* *h*, McKay *et al.*, *Trans. Faraday Soc.*, 1951, **47**, 428, 437; 1952, **48**, 997, 1099, 1103; 1954, **50**, 107.

numerals, and since preliminary experiments indicate that *cyclo*hexanone is more efficient than the other ketones it is included as the first member of the list. Arabic numerals in the Table refer to the order of solvent efficiency deduced from measurements by other workers. Wherever possible the order of solvents has been assigned on the basis of distribution ratios measured at a given acidity. In other cases it has been necessary to use reported values for percentage extractions, although such data are not strictly comparable because of different volume changes on equilibration. For these reasons no detailed evaluation of the results, *e.g.*, by statistical ranking methods, is justifiable; but it seems certain that the solvent order derived from the present experimental studies has some measure of generality and could be used as a guide to the choice of solvent, at least in the extraction of similar inorganic complexes.

Analytical Considerations.—The unfavourable volume changes which often occur on equilibration need not be a deterrent to the use of any particular solvent–acid system. Pre-treatment of either phase decreases the extent of volume changes at high initial acidities (Bock, Kusche, and Bock, *loc. cit.*), and miscibility may be decreased by the addition of salting out agents though these will certainly affect also the distribution ratios. An obvious device would be to alter the initial phase ratio from that employed in the present work.

Some of the solvents are not well suited to solvent-extraction procedures. Peroxidation was especially troublesome with 2 : 2′-dichlorodiethyl ether, but that of di*iso*propyl

ether can be retarded by catechol. Methyl *iso*butyl ketone is the most convenient of the lower ketones since methyl *iso*propyl ketone formed emulsions readily with 0·02—0·05N-hydriodic acid and with hydrochloric acid of moderate strength. While these always broke in 10 min., emulsions formed by methyl *n*-propyl ketone sometimes persisted for 2—4 hr. *n*-Butaldehyde emulsified so readily that its examination was discontinued. Hydrolysis of esters increased with acidity and in the order hydriodic > hydrobromic > hydrochloric acid : it was noticeably rapid with ethyl acetate, but this appeared to present no great practical disadvantages. The inconvenient preparation of hydriodic acid free from iodine can be avoided by the effective device which produces the acid and a salting-out agent *in situ* from a mixture of sulphuric acid and potassium iodide (Irving and Rossotti, *Analyst*, 1952, **77**, 801).

Indium has been shown to be essentially quantitatively extracted from hydriodic acid or hydrobromic acid into a large variety of solvents. By use of a suitable solvent quantitative extraction into hydrochloric acid is also possible. However, for the purpose of separations from other metals, the use of the less efficient solvents is to be preferred. Removal of iron from indium by extraction of the former from hydrochloric acid into diethyl ether (Milner, *ibid.*, 1951, **76**, 488) or di*iso*propyl ether (Maxwell, Haymond, Bemberger, Garrison, and Hamilton, *J. Chem. Phys.*, 1949, **17**, 1006) has been claimed under conditions where the present results indicate that indium is also extracted. The ready extraction of indium into ketones, and probably the ready extraction of a number of other metallic halides which are known to be extracted only to a small extent into diethyl ether, is likely to find increasing applications in analysis.

Formation of Three-phase Systems.—Three phases in equilibrium resulted from *iso*propyl ether and solutions of indium in hydriodic acid at initial acidities greater than 4·95N. Three phases have also been reported in the system *iso*propyl ether–hydrochloric acid containing gallium (Nachtrieb and Fryxell, *J. Amer. Chem. Soc.*, 1949, **71**, 4035) and iron (Dodson, Forney, and Swift, *ibid.*, 1936, **58**, 2573), and with zinc or cobalt in the system thiocyanic acid–diethyl ether (Bock, *Z. anal. Chem.*, 1951, **133**, 110). In these systems the appearance of the third phase seems to be associated with a high concentration of metal, though this cannot be the explanation in the present instance. Similarly two phases are formed by relatively concentrated solutions of silver perchlorate in benzene and toluene (Hill, *J. Amer. Chem. Soc.*, 1922, **44**, 1163) and by NH_4AlCl_4, NH_4GaCl_4, or $LiGaCl_4$ in diethyl ether (Friedman and Taube, *ibid.*, 1950, **72**, 3362). It has been suggested that such behaviour is characteristic of highly polar substances in solvents of low dielectric constant (Friedman and Taube, *loc. cit.*), and a thermodynamic explanation has been advanced (Nachtrieb and Fryxell, *ibid.*, 1949, **71**, 4035). In the present system, as with others reported above, the denser organic phase is found to contain more metal than the lighter. Laurene (Ph.D. Thesis, Rensselaer Polytechnic Inst., 1952) has suggested that the extracted species is more highly hydrated in the denser phase. While our measurements demonstrate the presence of more water in the denser phase, it is not established that the additional water is bound to the acido-complex.

Volume Changes on Equilibration.—In consequence of a measure of mutual solubility the equilibration of equal volumes of organic and aqueous phase generally leads to striking volume changes which depend upon the particular solvent, and the nature and concentration of the halogen acid (cf. Experimental section). The volume of the aqueous phase generally increases at the expense of that of the organic phase, as shown for various ketones in Fig. 8, and for various ethers in Fig. 3 of Part I. For any one solvent these volume changes are more marked in the order hydriodic > hydrobromic > hydrochloric acid. For any given acid they become less pronounced on ascending a homologous series. Volume changes with 2 : 2′-dichlorodiethyl ether are negligible; with *iso*pentyl alcohol and acetate at high acidities the organic phase increases at the expense of the aqueous phase.

Equilibrium Acidities.—One result of an increase in the volume of an aqueous phase on equilibration is that the final concentration of acid, N, is less than the initial value, N'. The partition of acid itself into the organic phase at high concentrations contributes something to this decrease in N, and except in the case of 2 : 2′-dichlorodiethyl ether and *iso*pentyl alcohol and acetate, the final equilibrium acidities pass through a maximum value.

Values of this maximum acidity, N, and the corresponding initial acidities, N', are given in Table 4. They represent the maximum acidities attainable in the aqueous phase, starting with equal volumes of aqueous acid and organic solvent neither of which has been pre-saturated (" conditioned ") with the other phase. Increase in initial acidity beyond these critical values will merely result in a rapid approach to the point where the phases become completely miscible.

TABLE 4. *The maximum acidities, N, obtainable in equilibration of equal volumes of organic solvent and acid of initial normality N'.*

Solvent	HCl		HBr		HI	
	N	N'	N	N'	N	N'
Diethyl ether	4·8	7·0	3·5	5·0	2·0	3·0
Di*iso*propyl ether	7·3	8·0	5·6	6·0	4·2	5·0
Methyl propyl ketone	3·9	6·0	2·5	3·5	1·4	2·0
Methyl *iso*propyl ketone	3·8	6·0	2·4	3·0	2·1	2·5
Methyl *iso*butyl ketone	6·4	7·0	4·6	6·0	3·0	4·0
Ethyl acetate	4·5	5·8	3·1	4·0	1·7	2·4

Water Content of the Organic Phases.—Determinations of the molar solubility of water in the organic phase after equilibration with hydrochloric and hydrobromic acid of various initial acidities are given for ethyl and *iso*pentyl acetate and pentyl alcohol, and diethyl and

FIG. 8. *Volume changes on equilibration of 20 ml. of ketone and 20 ml. of halogen acid.*

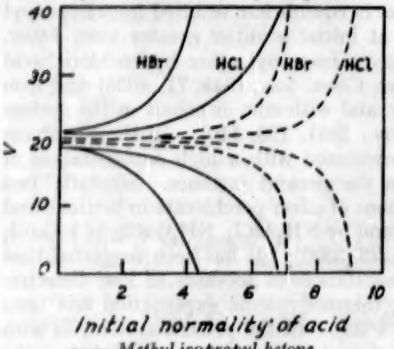
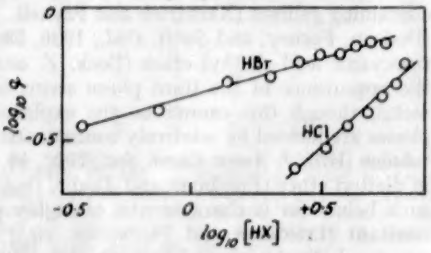


FIG. 9. *The extraction of halogen acids into isopentyl alcohol.*



di*iso*propyl ether in the Experimental section. Determinations of the solubility of water in the absence of acids agree well with values in the literature (Durrans, " Solvents," Chapman and Hall, London, 1950). The solubility of water in *iso*pentyl alcohol increases markedly with acidity but in the remaining solvents it first decreases with increasing acidity but eventually rises again.

Extraction of Halogen Acids.—Partial miscibility with water appears to be a necessary, but not a sufficient, condition for the extraction of halogen acids into organic solvents. Thus the efficiency of *iso*pentyl alcohol as an extractant for acids is very much greater than that of the ethers which, in turn, are more effective than the hydrocarbons and their halogen derivatives. A recent process for the recovery of hydrochloric acid from industrial wastes utilises extraction with pentanols (Crittendon and Hixson, *Ind. Eng. Chem.*, 1954, **46**, 265).

Fig. 9 shows the dependence of the distribution ratio, q, on equilibrium acidity for the extraction of hydrogen chloride and bromide into *iso*pentyl alcohol. If undissociated hydrogen halide undergoes partition and exists as such in the organic phase (cf. Everett and Rasmussen, *J.*, 1954, 2812), then from equation (15) of Part I we can deduce that

$$\partial \log q / \partial \log C_{HX} = \bar{h} - \bar{h} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where $\bar{h}$ and $\bar{h}$ are the ligand numbers of hydrogen in the organic and aqueous phase respectively. The experimental value of this derivative is 0·88 for hydrochloric acid, implying 12% of association in the aqueous phase, provided $\bar{h} = 1$. For hydrobromic acid the value of the gradient is only 0·29; but the association can scarcely be as high as 71% over the concentration range 0·5—9N. However, the derivation of equation (12) postulates that activity coefficients are constant throughout the range of acidities used, and that there are no changes of phase composition such as would invalidate the use of a constant stoicheiometric partition coefficient for the acids. Moreover there is evidence that hydrobromic acid is stronger than hydrochloric acid in aqueous solution (Ebert, *Naturwiss.*, 1925, **13**, 393; Robinson, *Trans. Faraday Soc.*, 1936, **32**, 743) and in glacial acetic acid (Bell and Skinner, *J.*, 1952, 2955; Kolthoff, *J. Amer. Chem. Soc.*, 1934, **56**, 1007). If this is true also in *iso*pentyl alcohol, *i.e.* if the acid is appreciably more dissociated in the organic phase, the lower value found for $\partial \log q/\partial \log C_{HBr}$ would be explicable, for the ligand number $\bar{h}$ in the organic phase would be less than unity (cf. Part I, equation 15).

For many other solvents investigated (but not reported here in detail) the partition of halogen acids at all moderate concentrations is so low that to a close approximation $NV = N'V'$. The amount of halogen acid extracted into diethyl and di*iso*propyl ether increases with increasing N', at first slowly and then rapidly above a critical concentration: even so the maximum value for the partition ratio is only $\sim 10^{-3}$ (Nachtrieb and Conway, *loc. cit.*; Bock, Kusche, and Bock, *loc. cit.*; Williams and Chalkley, Part II). While the addition of salts in macro-quantities is known to enhance the extraction of hydrochloric acid (Nachtrieb and Conway, *loc. cit.*; Garwin and Hixson, *Ind. Eng. Chem.*, 1949, **41**, 2298, 2303; Geankoplis and Garwin, *ibid.*, 1950, **42**, 1141) it can reasonably be assumed that the tracer quantities of indium used in the present experiments had comparatively little influence on the distribution of free acid and water in the system except in so far as water and halogen acid are involved in the formation of the extractable species and transported with it across the phase boundary. Variations in the distribution of acid and water can then be explained as follows.

According to Stokes and Robinson (*J. Amer. Chem. Soc.*, 1948, **70**, 1870) the hydration numbers of hydrochloric, hydrobromic, and hydriodic acid are 8·0, 8·6, and 10·6 respectively. Hence at concentrations of approximately 6, 5·5, and 4·4N respectively, all the water in such solutions will be effectively bound to the halogen acid. The withdrawal of water from the organic phase to solvate halogen acid should thus increase with concentration, as observed, up to certain critical values. At still higher concentrations the dissolved halogen acids could not be fully hydrated and the solvation sheaths would be completed by organic molecules (provided these have a sufficiently marked donor character) withdrawn from the organic phase. In view of the organic content of the aqueous phase the critical maximum acidities will differ from those estimated above for the pure acids and will depend on the nature of the organic solvent and the extent to which it can co-ordinate competitively with water to the particular halogen acid. Such factors are apparent in Table 4, for the maximum acidities, although invariably decreasing in the order HCl > HBr > HI, are not the same for any one acid. As increasing amounts of organic solvent dissolve in the aqueous phase its dielectric constant will fall. This will favour the association of hydrogen and halide ions and will thus increase the extraction of undissociated acid into the almost anhydrous organic phase. If the halogen acid is extracted as a hydrated ion-pair, much as is indium bromide which is shown to be extractable as the hydrated acido-complex $HInBr_4,10H_2O$ (Part III and IV), the amount of water in the organic phase will increase again.

Such explanations cannot be applied to the systems involving *iso*pentyl alcohol. Here volume changes are in the opposite sense to those previously discussed and large amounts of water and halogen acid pass into the organic phase as the initial acidity is increased. It appears that the solubility of water in *iso*pentyl alcohol is so high (in consequence of hydrogen bonding) that hydrated halogen acids are able to undergo partition freely, so that the distribution of both water and acid increases with increasing acidity. It has also been suggested that the presence of halogen acid lowers the difference in internal pressures

between aqueous and organic phases and so promotes miscibility (Crittendon and Hixson, *loc. cit.*; Reburn and Shearer, *J. Amer. Chem. Soc.*, 1933, **55**, 1774). The behaviour of *iso*pentyl acetate at high acidities is doubtless due to the production of *iso*pentyl alcohol by hydrolysis. Hydrolysis was also apparent in measurements with ethyl acetate, and since its extent will be a function of the duration of equilibration as well as of acidity the figures given for volume changes and water content have no absolute significance, though they indicate how the system behaves in certain circumstances.

The general treatment of solvent extraction outlined in Part I is only strictly applicable to "ideal systems" but its use in discussing the frequently highly "non-ideal" systems encountered in the solvent extraction of indium halides described in the present paper has at least permitted a semiquantitative interpretation of the results in most cases. While the results are of immediate analytical interest, it is clear that a complete understanding of the physical chemistry of an individual system can be achieved only through a detailed investigation from a more fundamental standpoint such as that adopted in the investigation of the physical chemistry of uranyl nitrate solutions (cf. McKay, *Chem. and Ind.*, 1954, 1549, and refs. therein).

We are indebted to A. Jenkins, B.A., for measurements of the solubility of water in some solvents, and of the partition of indium into furfuraldehyde and butaldehyde. Grateful acknowledgment is made to the Royal Society for the loan of apparatus, to Imperial Chemical Industries Limited for a grant towards the purchase of chemicals and radionuclides, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (F. J. C. R.).

INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

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Stereochemistry of the Side-chain of the Steroidal Sapogenins: New Isomers of the Normal- and iso-*Sapogenins.*

By R. K. CALLOW, D. H. W. DICKSON, J. ELKS, R. M. EVANS, V. H. T. JAMES, A. G. LONG, J. F. OUGHTON, and J. E. PAGE.

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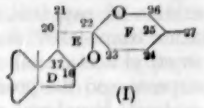
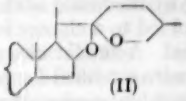
ψ-Sapogenins treated in solution with a trace of hydrochloric acid are converted by ring closure into isomers that are not identical with the original natural sapogenins. These *cyclo*-ψ-sapogenins are, under slightly acid conditions, in equilibrium with a small proportion of the open-chain ψ-sapogenins. Acetylation of the *cyclo*-ψ-compounds in pyridine gives monoacetates: boiling acetic anhydride yields diacetates of the ψ-compounds. Eight such *cyclo*-ψ-compounds have been prepared and their optical rotations and infrared absorption have been studied. The *cyclo*-ψ-compounds are believed to differ from the parent *iso*- or normal sapogenins only by virtue of stereoisomerism at $C_{(20)}$ or $C_{(22)}$ or both, but the configuration at these centres cannot yet be defined.

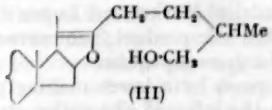
STEROIDAL sapogenins possessing the intact *spiro*ketal side chain were classified by Marker and his colleagues as "normal" or "*iso*" on the basis of their stability to acids; a normal sapogenin gave rise to the corresponding *iso*-sapogenin on long treatment with mineral acid. This classification is supported by the infrared spectra of the sapogenins; members of the normal series show in the 800—1100-cm.$^{-1}$ region a common absorption pattern that differs in detail from that displayed by the *iso*-compounds (Wall, Eddy, McClennan, and Klumpp, *Analyt. Chem.*, 1952, **24**, 1337; Jones, Katzenellenbogen, and Dobriner, *J. Amer. Chem. Soc.*, 1953, **75**, 158).

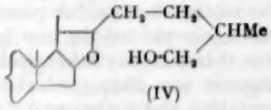
Corresponding members of the two series were thought to differ only in their configurations at $C_{(22)}$, as expressed in the partial formulæ (I) and (II) for the side-chains of the

normal and the *iso*-compounds respectively. The evidence for this rested on the interconversion of such isomers with mineral acid and on the reported identity of the *ψ*-sapogenins (III) and dihydrosapogenins (IV) obtained from isomeric pairs by treatment with acetic anhydride and by catalytic hydrogenation respectively (cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1949, p. 587; Shoppee and Shoppee, "Chemistry of Carbon Compounds," ed. E. H. Rodd, Vol. 2B, Elsevier, Amsterdam, 1953).


(I)


(II)


(III)


(IV)

In 1953 Scheer, Kostic, and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 4871) showed that, contrary to Marker's findings, sarsasapogenin (normal) and smilagenin (*iso*) furnished different *ψ*-sapogenins and dihydro-derivatives.* They isolated the $C_{(22)}$–$C_{(27)}$ chain of sarsasapogenin by degradation of the *ψ*-derivative and obtained (+)-α-methylglutaric acid; smilagenin, treated similarly, gave (−)-α-methylglutaric acid. It was thus demonstrated convincingly that the configuration at $C_{(25)}$ differs in the two sapogenins. It has been shown more recently, by similar means, that other normal sapogenins, *viz.*, *neo*tigogenin and sisalagenin (Callow and James, *J.*, 1955, 1671) belong to the same series as sarsasapogenin and that the *iso*-sapogenins, tigogenin, hecogenin, and diosgenin are similar to smilagenin in respect of configuration at $C_{(25)}$ (James, *Chem. and Ind.*, 1953, 1388; Callow and James, *loc. cit.*). The observation that samogenin and its normal isomer, markogenin, give different *ψ*-derivatives (Wall, Eddy, Serota, and Mininger, *J. Amer. Chem. Soc.*, 1953, **75**, 4437) is also in accordance with the generalisation that the normal and *iso*-sapogenins have opposite configurations at $C_{(25)}$ (cf. Farmer and Kon, *J.*, 1937, 414).

This conclusion calls for an explanation of the interconversion of normal and *iso*-compounds, which, it now appears, involves inversion at $C_{(25)}$, a centre that might be expected to be highly stable. A re-investigation of the conversion of normal into *iso*-sapogenins by mineral acid forms the subject of a separate paper (Callow and James, *loc. cit.*); we deal here with the alleged conversion of *ψ-iso*-sapogenins into a mixture of the corresponding normal and *iso*-compounds (Marker and Lopez, *J. Amer. Chem. Soc.*, 1947, **69**, 2373).

Observations made independently in our two laboratories led to a re-examination of the action of acid in trace amounts on *ψ*-sapogenins in solution and, as a result, new types of isomers have been discovered. Preliminary notes on this work have been published (Callow and James, *Chem. and Ind.*, 1954, 691; Dickson, Elks, Evans, Long, Oughton, and Page, *ibid.*, p. 692), and similar observations have been made in other laboratories on isomers of sarsasapogenin and smilagenin (Wall, Eddy, and Serota, *J. Amer. Chem. Soc.*, 1954, **76**, 2849; Wall and Serota, *ibid.*, p. 2850) and of diosgenin (Ziegler, Rosen, and Shabica, *ibid.*, p. 3865).

In one of our preliminary communications (Dickson *et al.*, *loc. cit.*) the name "*ana*"-sapogenin was suggested for the new isomers, which had then been obtained only in the *iso*-series. It is inappropriate to use the same name to cover the compounds since obtained from normal sapogenins, since there is certainly a difference in configuration at $C_{(25)}$ and there may be at $C_{(20)}$ or $C_{(22)}$. We would prefer, therefore, to adopt the suggestion made by Taylor (*Chem. and Ind.*, 1954, 1066) and to refer to the new isomers as *cyclo-ψ*-normal

* Trivial names are used for sapogenins throughout this paper; their constitutions are shown in Table 1.

or *cyclo-ψ-iso*-sapogenins; this nomenclature preserves the distinction between the $C_{(25)}$ isomers and, at the same time, suggests how the compounds arise.

Marker and Lopez (*loc. cit.*) treated a number of *ψ-iso*-sapogenins in ethanolic solution with hydrochloric acid, added to a concentration of about 0·5N, and kept the solutions overnight in a refrigerator. The products, precipitated by water and recrystallised, yielded *iso*-sapogenins, and from the mother-liquors were isolated "*neo*"-sapogenins, which had lower melting points and, refluxed with acetic anhydride, yielded acetates of "*neo*"(*i.e.*, normal)-sapogenins. Our own findings were in complete contrast. We observed, for example, that adding hydrochloric acid, to a concentration of, say, 0·01N, to a solution of *ψ*-hecogenin in ethanol led to a change in specific rotation from +100° to a steady value of +35·5° within 3 hours. A similar change occurred in ethyl acetate solution. The conditions of the reaction were modified for preparative purposes and the product was found to be a new isomer, *cyclo-ψ*-hecogenin; the only other material found was a small amount of hecogenin in the mother-liquors. A precise repetition of Marker and Lopez's experiment with *ψ*-hecogenin again yielded the new isomer as the sole product; no normal sapogenin could be found in this or in any other cyclisation of a *ψ-iso*-sapogenin.

cyclo-ψ-Hecogenin was distinguished from hecogenin by a lower melting point and a higher optical rotation and by many differences in the infrared absorption spectrum (see below).

cyclo-ψ-Hecogenin forms a monoacetate (presumably at the 3-hydroxy-group) on treatment with acetic anhydride and pyridine. The infrared spectra of the free alcohol and the acetate are similar in the 800—1000-cm.$^{-1}$ region. Elementary analysis of both alcohol and acetate indicates that *cyclo-ψ*-hecogenin is isomeric with *ψ*-hecogenin and hence with hecogenin itself.

cyclo-ψ-Hecogenin resembles hecogenin and differs from the open-chain *ψ*-compound in having no free hydroxyl group at $C_{(26)}$ (as shown by formation of a monoacetate), by its transparency at *ca.* 217 mμ (cf. Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, in the press) and by its failure to give a colour with tetranitromethane. The ease of formation of *cyclo-ψ-* from *ψ*-hecogenin is best explained by assuming that it arises by reclosure of ring F to give a *spiro*ketal differing from the parent *iso*-sapogenin only in the configuration at $C_{(20)}$ or $C_{(22)}$ or both.

cyclo-ψ-Hecogenin is efficiently converted into hecogenin by brief treatment with boiling alcoholic hydrogen chloride. On treatment with boiling acetic anhydride, it gives a high yield of *ψ*-hecogenin diacetate; in this behaviour it differs from the *iso*-sapogenin, which requires prolonged treatment with acetic anhydride at about 200° to produce the *ψ*-derivative.

When *ψ*-tigogenin, 11-oxo-*ψ*-tigogenin, *ψ*-smilagenin, and *ψ*-diosgenin (all *ψ-iso*-sapogenins) were submitted to mild acid treatment, they too yielded *cyclo-ψ*-compounds with properties, both physical and chemical, similar to those of *cyclo-ψ*-hecogenin. In particular, all the *cyclo-ψ-iso*-sapogenins showed characteristic infrared absorption between 800 and 1100 cm.$^{-1}$. This is discussed in more detail below.

When ethanolic solutions of *ψ*-normal sapogenins were treated with a trace of acid only small, or even undetectable, changes in optical rotation occurred within a short period. Nevertheless, addition of water caused precipitation of *cyclo-ψ*-compounds with optical rotations similar to those of the *ψ*-compounds from which they were derived. The *cyclo-ψ*-compounds of the normal series have a characteristic type of infrared absorption spectrum different from that of the *cyclo-ψ-iso*-derivatives. Like the latter, they yield diacetates of the parent *ψ*-sapogenins when refluxed with acetic anhydride, and monoacetates of *cyclo-ψ*-sapogenins with acetic anhydride in pyridine. When they are boiled with dilute hydrochloric acid the normal sapogenins are obtained. *cyclo-ψ*-Sarsasapogenin, *cyclo-ψ-neo*tigogenin, and *cyclo-ψ*-sisalagenin were prepared from the corresponding *ψ*-compounds and are described in the Experimental section.

A study of the properties of solutions of *ψ*- and *cyclo-ψ*-sapogenins has disclosed the existence in acid medium of an equilibrium between the two types. Acidification of an alcoholic solution of either *ψ*-hecogenin or *cyclo-ψ*-hecogenin caused the rotation to change to an intermediate value, corresponding to about 1 part of the former and 9 of the latter.

A similar observation was made with 11-oxotigogenin derivatives. In the normal series, the rotations of the *ψ*- and *cyclo-ψ*-compounds were too close together to allow the method to be used.

Again, acidification of an alcoholic solution of 11-oxo*cyclo-ψ*-tigogenin caused the appearance of an absorption maximum at 216 mμ with about one-tenth of the intensity of that of 11-oxo-*ψ*-tigogenin; a solution of the latter, on acidification, gave the same reduced absorption. The pair of isomers derived from sarsasapogenin behaved similarly, indicating that the same equilibrium exists in the normal series. With other compounds results were less clear cut; the same general effect was noted, but the weak maxima were either displaced or obscured by an increased general absorption.

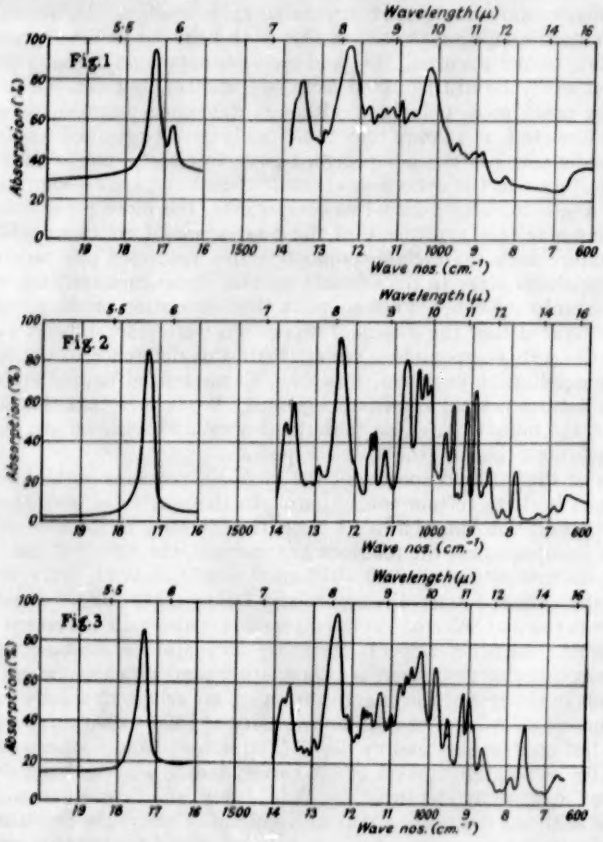
Further evidence came from paper-chromatographic studies. In neutral or pyridine-containing solvents the sapogenins used in this work behaved in the expected manner as pure compounds: isomeric normal, *iso*-, and *cyclo-ψ*-compounds differing only in the side chains could not easily be distinguished from one another, but the *ψ-iso*- and *ψ*-normal compounds were much more polar and, although differences between them individually could hardly be observed, as a group they could easily be distinguished from the other four isomers. In acidic solvents the *ψ*-sapogenins gave two spots, one behaving like the *ψ*-compound, the other like the *cyclo-ψ*-compound. Similarly, *cyclo-ψ*-compounds could be resolved under these conditions into two components, the more polar behaving as a *ψ*-compound. This is further evidence that the *ψ*-sapogenins form in an acidic medium an equilibrium mixture with the *cyclo-ψ*-compounds and confirmed our previous conclusion that the latter predominate. In the solvents used for chromatography the transformation of one compound into the other is not so quick that separation of the components is prevented, but we noticed that the *ψ*-normal sapogenins were more difficult to trace in such mixtures than the *ψ-iso*-compounds. We attribute this difference to the further changes suffered by the equilibrium mixtures, which are themselves of limited stability and pass finally into the natural normal and *iso*-sapogenins. We believe that this state is reached more rapidly in the normal series, so that the *ψ*-normal sapogenins are more difficult to detect in acid solutions than are the *ψ-iso*-compounds.

Comparison of the infrared spectra of the *cyclo-ψ*-sapogenins with those of the other classes of isomers leads to certain conclusions. In the spectra of normal sapogenins the 920—915-cm.$^{-1}$ absorption band has 3—4 times the intensity of the 899—894-cm.$^{-1}$ band, whereas in the *iso*-compounds the relations are reversed, the 899—897-cm.$^{-1}$ band having 1·3—2·5 times the intensity of the 920—916-cm.$^{-1}$ band (see Wall, Eddy, McClennan, and Klumpp, *loc. cit.*; Jones, Katzenellenbogen, and Dobriner, *loc. cit.*). Bands at 851 cm.$^{-1}$ in the normal series and at 863 cm.$^{-1}$ in the *iso*-series are also valuable means of distinguishing between them. In other respects there are no major differences. In the *ψ*-series, the type of absorption changes; there is a dominating band with a maximum at 1045—1030 cm.$^{-1}$, and bands in the rest of the fingerprint region are relatively subdued particularly at the lower frequencies. A band of medium intensity at 1695—1690 cm.$^{-1}$ (olefinic ether) is characteristic, but may be obscured by the C=O stretching band in the spectra of ketonic compounds. The absorption spectra of the corresponding *ψ*-normal and *ψ-iso*-sapogenins were said to be "essentially identical" by Wall, Eddy, and Serota (*loc. cit.*). We should agree with this, with the reservation that in Nujol mulls, where the crystalline structure is retained, differences may be considerable. This was observed, for instance, with *ψ*-hecogenin and *ψ*-sisalagenin diacetates. These compounds are sufficiently soluble for measurements to be made in solution at concentrations at which "essential identity" of absorption could be confirmed.

In contrast to the other classes of isomers, the *cyclo-ψ*-sapogenins show distinct differences between the normal and the *iso*-series. The fingerprint region shows a series of sharp, well-defined peaks, indicating the closure, from the open-chain *ψ*-compound, of a ring system with structure analogous to, but not identical with, that in the original sapogenins. In both normal and *iso*-series the bands at 920—916 and at 902—892 cm.$^{-1}$, present in the original sapogenins and lost in the *ψ*-compounds, reappear in the *cyclo-ψ*-compounds, but are then of nearly equal intensity in both series. The *cyclo-ψ-iso*-compounds show characteristic absorption peaks at about 1360, 1070, 1012, 920, 895, 856, and

785 cm.$^{-1}$, and the *cyclo*-ψ-normal compounds at about 1360, 1080, 1048, 982, 916, 901, and 868 cm.$^{-1}$. The two types of spectra are sufficiently distinct to indicate that some factor of structure or interaction of groups differs in the normal and the *iso*-series. The features discussed are illustrated by the representative spectra of ψ-tigogenin diacetate (Fig. 1, C.S. No. 202 *), *cyclo*-ψ-tigogenin acetate (Fig. 2, C.S. No. 203) and *cyclo*-ψ-*neo*tigogenin acetate (Fig. 3).

Infrared spectra of: FIG. 1, *ψ-Tigogenin diacetate;* FIG. 2, cyclo-*ψ-tigogenin acetate;* FIG. 3, cyclo-ψ-neo-*tigogenin acetate. All* 1% *solutions in* CS_2; 0·8 *mm. cell; Perkin–Elmer double-beam spectrophotometer with a sodium chloride prism.*



The optical properties of our compounds are presented in Table 1. The values of $\Delta[M]$ for the change sapogenin ⟶ *cyclo*-ψ-sapogenin vary little for the normal compounds, but cover a rather wider range in the *iso*-series. Nevertheless, there is an obvious difference between the values in the two series, a fact made the more remarkable by the close similarity between $\Delta[M]$ values for the change sapogenin ⟶ ψ-sapogenin in both of the series. The significance of these results is discussed below.

To return to the work of Marker and Lopez (*loc. cit.*), it is apparent that they did not

* Spectra thus denoted have been deposited with the Chemical Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained from the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1, on application stating the C.S. No.

TABLE 1. *Specific rotations and molecular rotation differences of steroid sapogenins, ψ-sapogenins, and* cyclo-*ψ-sapogenins.*

Parent compounds (*A*) Name	Substituents	$[\alpha]_D$	*ψ*-Isomers (*B*) $[\alpha]_D$	*cyclo-ψ*-Isomers (*C*) $[\alpha]_D$	$\Delta[M_D]$ *B* − *A*	$\Delta[M_D]$ *C* − *A*
iso-*Sapogenins* (25 *D*) *						
Smilagenin	3β-OH; 5β-H	− 67°	+ 24°	− 61°	+378°	+ 25°
Tigogenin	3β-OH; 5α-H	− 67	+ 23	− 67·5	+375	− 2
11-Oxotigogenin ...	3β-OH; 5α-H; 11-O:	− 33	+ 76	− 29	+469	+ 17
Hecogenin	3β-OH; 5α-H; 12-O:	+ 7	+100	+ 21	+400	+ 62
Diosgenin	3β-OH; Δ⁵	−123	− 28	−113	+393	+ 41
Normal sapogenins (25 *L*)						
Sarsasapogenin ...	3β-OH; 5β-H	− 77	+ 12	+ 27	+370	+432
*neo*Tigogenin	3β-OH; 5α-H	− 75	+ 11	+ 25	+358	+416
Sisalagenin	3β-OH; 5α-H; 12-O:	− 3	+ 91	+ 95	+411	+428

Mean values: $\Delta[M_D]$ (*B* − *A*) { *iso*-sapogenins ..... +404°; normal sapogenins ..... +380

$\Delta[M]_D$ (*C* − *A*) { *iso*-sapogenins ..... + 29; normal sapogenins ..... +425

For the three epimeric pairs: $\Delta[M_D]$ {25 *D* minus 25 *L*} { sapogenins ..... + 41; *ψ*-sapogenins ..... + 46; *cyclo-ψ*-sapogenins ..... −410

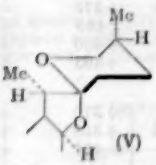
* In common with other workers in this field we have related the configuration at $C_{(25)}$ to that of the α-methylglutaric acid obtained by oxidation, and adopted the convention, currently accepted for α-substituted acids, of using the prefixes *D*- and *L*- (cf. James, *loc. cit.*, Ziegler *et al.*, *loc. cit.*, Klyne and Stokes, *J.*, 1954, 1979; Dickson, Page, and Rogers, *J.*, 1955, 443; Ziegler, Rosen, and Shabica, *J. Amer. Chem. Soc.*, 1955, **77**, 1223; Bijvoet, *Endeavour*, 1955, **14**, 71).

obtain the *cyclo-ψ*-isomers upon cyclisation of their *ψ-iso*-sapogenins. This is suggested by the difference in melting point between their product and ours in, for example, the cyclisation of *ψ*-hecogenin, but more cogent evidence comes from the fact that their method of acetylation (boiling with acetic anhydride) would have converted any *cyclo-ψ-iso*-compounds into the *ψ-iso*-sapogenin diacetates, which would have been unmistakable both from their low melting points and from their elementary analyses. We can offer no explanation for the differences between their results and ours, and because of these differences we can throw no light upon the remarkably ready inversion at $C_{(25)}$ implied by their work.

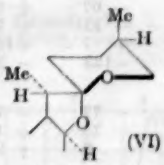
Two views have been expressed as to the structures of these new isomers. Wall, Eddy, and Serota (*J. Amer. Chem. Soc.*, 1954, **76**, 2849; cf. also Wall and Serota, *ibid.*, p. 2850), from a consideration of the reactions of the various isomers, have put forward the structures (V), (VI), (VII), and (VIII) for the side chains of the normal, *iso*-, *cyclo-ψ*-normal, and *cyclo-ψ-iso*-compounds respectively. Taylor (*loc. cit.*), on the other hand, on the basis of conformational analysis, and considering the probable mechanism of cyclisation of *ψ*-sapogenins, has assigned structures (V), (IX), (X), and (VIII) to the respective isomers; a similar view is taken by Ziegler, Rosen, and Shabica (*loc. cit.*) about their cyclisation of *ψ*-diosgenin. (These authors, following Marker, call their product "neodiosgenin" but it appears to be identical with our *cyclo-ψ*-diosgenin and is distinguished from yamogenin, the normal isomer of diosgenin, by the quoted infrared bands; cf. Jones *et al.*, *loc. cit.*)

The existing evidence does not appear to be convincingly in favour of either of these theories but some of Wall's reasoning, in particular, is made untenable by our demonstration of the equilibrium between *ψ*- and *cyclo-ψ*-compounds in acid (including acetic acid) solution. Thus, Wall uses in his argument the facts that *cyclo-ψ*-compounds are much more readily oxidised by chromic acid than are the sapogenins themselves and again that the dihydrocompounds obtained by catalytic reduction of *cyclo-ψ*-compounds are less stable to chromic acid than are the dihydrosapogenins. However, in view of our findings it cannot be said that *cyclo-ψ*-compounds, as such, have ever been oxidised or reduced; their apparent reactions are a most certainly those of the corresponding *ψ*-compounds in which the asymmetry at $C_{(20)}$ and $C_{(22)}$ is lost. For this reason, arguments based on the reactions of the dihydro-*cyclo-ψ*-compounds or of the *cyclo-ψ*-compounds in acid medium have no bearing on the configuration of the latter compounds at $C_{(20)}$ or $C_{(22)}$. We can add our own

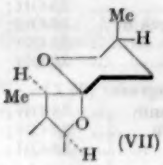
observations on the hydrogenation of *cyclo-ψ*-compounds. Hydrogenation of *cyclo-ψ*-tigogenin acetate in acetic acid containing sodium acetate was similar to that of *ψ*-tigogenin in being rapid and in giving (after acetylation) the same product. Hydrogenation of tigogenin acetate was very slow and gave a different dihydro-compound (cf. Wall, Eddy, and Serota, *loc. cit.*). We have attempted to carry out the reductions in neutral medium, but without success.


(V)

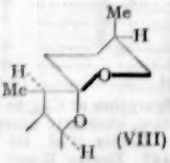
Wall: normal
Taylor: normal


(VI)

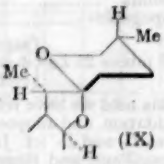
Wall: *iso*


(VII)

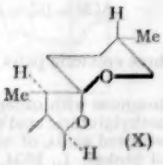
Wall: *cyclo-ψ*-normal


(VIII)

Wall: *cyclo-ψ-iso*
Taylor: *cyclo-ψ-iso*


(IX)

Taylor: *iso*


(X)

Taylor: *cyclo-ψ*-normal

We have examined the optical properties of our compounds to see whether they lend support to one or other of the above views. The similarity in the values of $\Delta[M]$ for the changes *iso-* ⟶ *ψ-iso-* (+404°) and normal ⟶ *ψ*-normal sapogenins (+380°) is in accord with Taylor's formulation, if the asymmetric centre at $C_{(25)}$ is assumed to exert no marked vicinal effect; however, after making this assumption it is difficult to reconcile Taylor's view with the very different values of $\Delta[M]$ for the changes sapogenin ⟶ *cyclo-ψ*-sapogenin in the two series (+29° and +425°, respectively) since in each precisely similar changes are involved at $C_{(20)}$ and $C_{(22)}$.

It would, perhaps, be possible to reconcile the molecular-rotation data with the scheme of Wall *et al.*, if it were to be supposed that the vicinal action of the 22-O- and the 20-Me group was of the same order of magnitude as that of the 6-O- and $C_{(4)}$ in 6-acetoxyl derivatives of coprostane and cholestane, in which the relative disposition of the groups is analogous. By use of Barton and Klyne's mean figures (*Chem. and Ind.*, 1948, 755) it is seen that the change of $C_{(4)}$ from α to β in the 6α-acetoxy-compounds entails a change of +291° in $[M]$, whereas change of $C_{(4)}$ from α to β in the 6β-acetoxy-compounds entails a change of −44°. However, the analogy that has been drawn is rather an example of the surprising effects of "vicinal action"—a phenomenon not susceptible to quantitative assessment—than an argument for the scheme of Wall *et al.*

It appears to us that the existing evidence permits the assignment of configurations to $C_{(16)}$, $C_{(17)}$, and $C_{(25)}$ only, of the asymmetric centres in rings E and F. The configurations of the normal and the *iso*-sapogenins at $C_{(25)}$, which have been discussed above, seem beyond dispute. Marker and Turner (*J. Amer. Chem. Soc.*, 1941, **63**, 767) have converted diosgenin into cholesterol by reactions that probably do not involve $C_{(17)}$ and therefore suggest that the former, in common with all the naturally occurring sterols, has its side chain attached in the β-configuration to that carbon atom. We do not, however, agree with Wall, Eddy, and Serota (*loc. cit.*) that identity of configuration at $C_{(20)}$ is also implied: the reactions involved the Clemmensen reduction of the latent $C_{(22)}$ carbonyl group of diosgenin and if that group existed, even transitorily, isomerisation at the neighbouring asymmetric centre would clearly be possible.

Scheer, Kostic, and Mosettig (*loc. cit.*), by proving that dihydrosarsasapogenin and

dihydrosmilagenin differ only at $C_{(25)}$, have shown that the parent sapogenins (and, by inference, normal and *iso*-sapogenins, in general) have identical configurations at $C_{(16)}$, $C_{(17)}$, and $C_{(20)}$; the situation is less clear at $C_{(22)}$, where inversion might have occurred during cleavage of the $C_{(22)}$–O bond (cf. Wall and Serota, *loc. cit.*).

Finally, it has been reasoned by Mueller, Stobaugh, and Winniford (*J. Amer. Chem. Soc.*, 1953, **75**, 4888) that the β-configuration at $C_{(17)}$ fixes the configuration at $C_{(16)}$ as β also. Since the transformations, sapogenin $\rightleftharpoons$ ψ-sapogenin $\rightleftharpoons$ *cyclo*-ψ-sapogenin would be expected to involve only the asymmetric centres at $C_{(20)}$ and $C_{(22)}$, we believe that normal and *cyclo*-ψ-normal sapogenins have the configuration 16β : 17β : 25*L* and that the *iso*- and *cyclo*-ψ-*iso*-compounds have the configuration 16β : 17β : 25*D*. The evidence as to configuration at $C_{(20)}$ and $C_{(22)}$ rests on much less firm foundations and has, indeed, led to contradictory opinions; we consider, therefore, that in the absence of direct evidence it is premature to assign configurations at these centres to any of the isomers.

Added in Proof.—Scheer, Kostik, and Mosettig ((*J. Amer. Chem. Soc.*, 1955, **77**, 641), Ziegler, Rosen, and Shabica (*ibid.*, p. 1223), and Wall, Serota, and Eddy (*ibid.*, p. 1230) have reported results of experiments on the sapogenin side-chain which do not differ in principle from their earlier results referred to in this paper.

Experimental

M. p.s were taken on a Kofler block and are corrected. Ultraviolet absorptions were determined on ethanol solutions and optical rotations on chloroform solutions unless otherwise specified.

Infrared absorptions were determined on two Perkin–Elmer Model 21 double-beam spectrophotometers with rock-salt prisms. In one laboratory the potassium bromide disc method was used as a routine, and most of the spectrograms deposited with the Society are taken by this method. In the other laboratory, solutions in CS_2 and CCl_4 were measured wherever possible; less soluble materials were examined as mulls in Nujol or in solution in bromoform, chloroform, or pyridine. Where measurement in CS_2 was possible, only figures for this solution are given, unless other media gave notably different results. Solvent absorption masked absorption peaks in some instances, but sufficient characteristic bands could be observed to identify the various classes of isomers.

The preparation of the ψ-sapogenins used in this work is described in the papers of Cameron *et al.* and of Callow and James (*locc. cit.*).

Treatment of ψ-Hecogenin with Hydrochloric Acid by the Method of Marker and Lopez (loc. cit.).—A solution of ψ-hecogenin (4 g.) in ethanol (100 ml.) and concentrated hydrochloric acid (4 ml.) was left overnight at 0°; some crystalline solid separated during this time. The mixture was poured into water. The precipitated solid crystallised from methanol as plates (3·08 g.), m. p. 190—196°, $[\alpha]_D^{22}$ +12·5°, the infrared spectrum of which indicated that they were essentially *cyclo*-ψ-hecogenin (see below): further crystallisation from slightly alkaline methanol gave the pure methanol solvate, m. p. 218—221°, $[\alpha]_D^{20}$ +18·5°.

The filtrate from the precipitated material was evaporated; the residue (0·86 g.) had the characteristic infrared absorption of a *cyclo*-ψ-sapogenin and yielded ψ-hecogenin diacetate on being boiled with acetic anhydride.

Preparation of cyclo-*ψ-Sapogenins.*—Cyclisation of ψ-sapogenins was carried out in ethanol or ethyl acetate. Both methods are exemplified for ψ-hecogenin; the other ψ-compounds were cyclised by essentially the same techniques, except in the few cases where differences are noted.

cyclo-*ψ-Hecogenin.*—(*a*) ψ-Hecogenin (7·3 g.) was dissolved in ethanol (100 ml.), and N-hydrochloric acid (1 ml.) was added. Crystallisation of the product began almost at once. After 30 min. the solid was collected (5·1 g.; m. p. 206—217°), and a further crop (1·6 g.) obtained by dilution of the filtrate with water.

(*b*) A solution of ψ-hecogenin (5 g.) in ethyl acetate (250 ml.), which had $[\alpha]_D^{20}$ +86°, was treated with one drop of concentrated hydrochloric acid, and the mixture was shaken. Within a minute $[\alpha]_D^{20}$ had fallen to +17° and was stable at this value. After being washed with water (3 × 250 ml.), the solution was evaporated on the water-bath under reduced pressure to the point of crystallisation, and the crystalline product was collected.

cyclo-*ψ-Hecogenin* separated from methanol with solvent of crystallisation (removed at 130°/0·5 mm. in 2 hr.), and the crystals had m. p.s depending on the rate of heating, *e.g.*, 221—

231° or 210—222°. From ethanol it separated in needles containing 1 mol. of ethanol, m. p. 196—212° after a change of crystal form at 145° (Found, in air-dried substance: C, 73·4; H, 10·0; after drying at 136°/0·2 mm.: C, 74·8; H, 9·85. $C_{27}H_{42}O_4,C_2H_6O$ requires C, 73·1; H, 10·15. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). $[\alpha]_D^{20}$ was +21°, $[\alpha]_{5461}^{21}$ +29° (*c*, 1·153), and $[\alpha]_D^{22}$ +22°, $[\alpha]_{5461}^{21}$ +29° (*c*, 0·565 in EtOH). The substance showed no appreciable absorption in the ultraviolet region above 205 mμ. Infrared max. (in CS_2) were at 3620, 1036 (equatorial hydroxyl), 1708 (ketone), 1068, 1012, 922, 895, 856, and 785 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin). Spectrum in KBr: (C.S. No. 176). The substance gave no colour with tetranitromethane.

The *acetate* was prepared by keeping a solution in acetic anhydride and pyridine (1 : 1) overnight at room temperature. From methanol or ethyl acetate it formed crystals with m. p. dependent on the rate of heating, 205—208° or 215—223°, $[\alpha]_D$ +9° (Found: C, 74·0; H, 9·4. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). $\nu_{max.}$ (in CS_2): 1735 and 1235 cm.$^{-1}$ (acetate), and the characteristic bands found in the alcohol.

Formation of ψ-Hecogenin Diacetate from cyclo-*ψ-Hecogenin.*—*cyclo-ψ*-Hecogenin (0·5 g.) in acetic anhydride (20 ml.) was boiled under reflux for 45 min. The solvent was then evaporated and the residue crystallised from methanol to give *ψ*-hecogenin diacetate (0·41 g.) as plates, m. p. 94—96°, $[\alpha]_D^{20}$ +71° (*c*, 0·56), identified by mixed m. p. and infrared spectrum (C.S. No. 188) (Found: C, 72·5; H, 9·1. Calc. for $C_{31}H_{46}O_4$: C, 72·3; H, 9·0%).

Formation of Hecogenin from cyclo-*ψ-Hecogenin.*—*cyclo-ψ*-Hecogenin (0·25 g.) in methanol (25 ml.) with concentrated hydrochloric acid (2·5 ml.) was boiled under reflux for 30 min. On cooling, hecogenin (0·23 g.) crystallised in plates, m. p. 260—263°, $[\alpha]_D^{22}$ +7° (*c*, 0·81), identified by mixed m. p. and infrared spectrum.

cyclo-*ψ-Smilagenin.*—This was prepared from *ψ*-smilagenin by method (*a*), and by method (*b*) but in methyl acetate. *cyclo-ψ*-Smilagenin separated from methanol as plates, m. p. 111—115°, resolidifying and melting at 183—186·5°, $[\alpha]_D^{21}$ −61°, $[\alpha]_{5461}^{21}$ −72° (*c*, 0·394). $\nu_{max.}$ (in KBr) 1365, 1075, 1015, 919, 897, 858, and 785 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin) (C.S. No. 177). Wall, Eddy, and Serota (*loc. cit.*) give m. p. 185° and $[\alpha]_D^{25}$ −60° for their "20-*iso*smilagenin." Another specimen of *cyclo-ψ*-smilagenin separated from acetone in small rhombs, m. p. 157—165°, $[\alpha]_D^{22}$ −65° (*c*, 1·0). It was characterised by its infrared spectrum and analysis (Found: C, 77·9; H, 10·7. Calc. for $C_{27}H_{44}O_3$: C, 77·8; H, 10·65%).

The acetate separated from *n*-hexane–ethyl acetate as small rhombs, m. p. 135—142°, $[\alpha]_D^{22}$ −53° (*c*, 1·01) (Found: C, 75·8; H, 10·2. Calc. for $C_{29}H_{46}O_4$: C, 75·9; H, 10·1%). $\nu_{max.}$ (in CS_2) 1730 and 1230 (acetate), 1070, 1018, 920, 895, 856, and 785 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin). Another specimen separated from methanol as plates, m. p. 151—154°, $[\alpha]_D^{21}$ −55°, $[\alpha]_{5461}^{21}$ −63° (*c*, 0·192). Wall, Eddy, and Serota (*loc. cit.*) give m. p. 160°, $[\alpha]_D^{25}$ −49°.

cyclo-*ψ-Tigogenin.*—This was prepared from *ψ*-tigogenin by method (*b*), the specific rotation dropping from +22·5° to −54°. cyclo-*ψ-Tigogenin* crystallised from methanol in needles (61% yield), m. p. 198—202°, $[\alpha]_D^{20}$ −67·5° (*c*, 0·64) (Found: C, 77·8; H, 10·75%). $\nu_{max.}$ (in Nujol) 3500 (OH), 1071, 1015, 920, 894, 857, and 787 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin). Spectrum in KBr: (C.S. No. 178).

The *acetate* formed plates (from methanol), m. p. 177—179°, $[\alpha]_D^{20}$ −71° (*c*, 0·69) (Found: C, 76·1; H, 10·3. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%). $\nu_{max.}$ (in CS_2) 1730, 1240 (acetate), 1068, 1012, 920, 893, 854, and 788 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin) (Fig. 2, C.S. No. 203).

Boiled under reflux with acetic anhydride, *cyclo-ψ*-tigogenin yielded *ψ*-tigogenin diacetate as a gum which had the infrared absorption characteristics of the authentic substance, and gave, on hydrolysis, *ψ*-tigogenin, m. p. and mixed m. p. 182—187°.

Boiling methanolic hydrochloric acid converted *cyclo-ψ*-tigogenin into tigogenin.

11-*Oxo*cyclo-*ψ-tigogenin.*—Prepared from 11-oxo-*ψ*-tigogenin in 73% yield by method (*b*) in methyl acetate, and precipitated by addition of aqueous sodium acetate, 11-*oxo*cyclo-*ψ-tigogenin* crystallised from ethanol in prisms, m. p. 223—226°, $[\alpha]_D^{21}$ −28° (*c*, 0·994) (Found: C, 75·5; H, 9·7. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). $\nu_{max.}$ (in CS_2) 3620 and 1035 (equatorial OH), 1707 (ketone), 1070, 1012, 918, 895, 855, and 784 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin). Spectrum in KBr, C.S. No. 179.

The *acetate* separated from ethyl acetate in leaflets with m. p. 207—223°, depressed on admixture with 11-oxotigogenin acetate, and $[\alpha]_D^{20}$ −40° (*c*, 1·08) (Found: C, 73·9. H, 9·2. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). $\nu_{max.}$ (in CS_2) 1731, 1235 (acetate), 1709 (ketone), 1070, 1012, 917, 892, 854, and 784 cm.$^{-1}$ (*cyclo-ψ-iso*-sapogenin).

11-Oxo*cyclo-ψ*-tigogenin was converted by boiling acetic anhydride into 11-oxo-*ψ*-tigogenin diacetate and by boiling methanolic hydrochloric acid into 11-oxotigogenin, both products being identified by comparison with authentic specimens.

In another preparation of 11-oxo*cyclo*-ψ-tigogenin, the conditions were those of Marker and Lopez (*loc. cit.*) (see above). The crystals which separated from solution were the *cyclo*-ψ-compound (60% yield after recrystallisation): the residue after evaporation of the mother-liquors was 11-oxotigogenin since, on being refluxed with acetic anhydride for 30 min., it yielded 11-oxotigogenin acetate (11%), m. p. 220—224°, $[\alpha]_D^{22}$ −40° (*c*, 1·0), identified by mixed m. p. and infrared spectrum.

cyclo-ψ-*Diosgenin*.—This was prepared from ψ-diosgenin by method (*a*) in 92% yield. Recrystallised from acetone, it formed needles, m. p. 193—198°, $[\alpha]_D^{22}$ −122° (*c*, 0·53). $\nu_{max.}$ (in CS_2) 3620 and 1042 (equatorial OH), 1665 and 835 (trisubstituted ethylene), 1072, 1012, 920, 895, 855, and 788 cm.$^{-1}$ (*cyclo*-ψ-*iso*-sapogenin). Spectrum in KBr, C.S. No. 180. Ziegler *et al.* (*loc. cit.*) give m. p. 197—201°, $[\alpha]_D$ −122°, for their "neodiosgenin," prepared from ψ-diosgenin by mild acid treatment. A specimen labelled "ψ-nitogenin" from the collection of the late Professor G. A. R. Kon (cf. Kon and Weller, *J.*, 1939, 800; Marker, Wagner, Goldsmith, Ulshafer, and Ruof, *J. Amer. Chem. Soc.*, 1943, **65**, 1248) was found to consist of *cyclo*-ψ-diosgenin. Recrystallised twice from acetone, it gave needles, m. p. 186—191°, $[\alpha]_D^{21}$ −120° (*c*, 0·985) (Found: C, 78·3; H, 10·0. Calc. for $C_{27}H_{42}O_3$: C, 78·2; H, 10·2%). Its infrared spectrum in CS_2 was identical with that of *cyclo*-ψ-diosgenin, prepared as above.

The *cyclo*-ψ-diosgenin gave a colour with tetranitromethane and a positive Liebermann–Burchardt test.

The *acetate* formed leaflets (from ethyl acetate), m. p. 183—212° (transition at 165°), $[\alpha]_D^{21}$ −118° (*c*, 0·51) (Found: C, 76·4; H, 9·5. $C_{29}H_{44}O_4$ requires C, 76·3; H, 9·7%). $\nu_{max.}$ (in CS_2) 1732 and 1238 (acetate), 1665 and 835 (trisubstituted ethylene), 1072, 1014, 918, 894, 855, and 786 cm.$^{-1}$ (*cyclo*-ψ-*iso*-sapogenin).

cyclo-ψ-Diosgenin was converted by boiling acetic anhydride into ψ-diosgenin diacetate and by boiling ethanolic hydrochloric acid into diosgenin, the products being identified by comparison with authentic specimens.

cyclo-ψ-*Sarsasapogenin*.—This was prepared from ψ-sarsasapogenin by method (*a*), the product being precipitated after 10 min. by addition of water. The precipitate, at first oily, slowly solidified and was recrystallised from methanol, from which it separated in needles, m. p. 99—102°, then resolidifying and melting at 172—179°, $[\alpha]_D^{18}$ +27°, $[\alpha]_{5461}^{18}$ +31° (*c*, 0·679) (Found, in air-dried substance: C, 75·6; H, 10·7; and, after drying at 100°/0·1 mm.: C, 78·3, 78·3; H, 11·3, 10·8. Calc. for $C_{27}H_{44}O_3,CH_4O$: C, 74·95; H, 10·8. Calc. for $C_{27}H_{44}O_3$: C, 77·8; H, 10·65%). $\nu_{max.}$ (in CS_2) 3620, 1030 (axial OH), 1360, 1080, 1046, 982, 917, 902, and 869 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin). Spectrum in KBr, C.S. No. 181. The equal intensity of the bands at 917 and 902 cm.$^{-1}$ is to be noted. Wall, Eddy, and Serota (*loc. cit.*) report m. p. 176—177°, $[\alpha]_D^{25}$ +31·9°.

cyclo-ψ-Sarsasapogenin could not be prepared by method (*b*): the product was sarsasapogenin, and this result seems to be an indication of the greater instability of *cyclo*-ψ-normal as compared with the *cyclo*-ψ-*iso*-compounds.

cyclo-ψ-Sarsasapogenin acetate separated in plates from methanol, m. p. 167—170°, $[\alpha]_D^{19}$ +27°, $[\alpha]_{5461}^{19}$ +32° (*c*, 0·515) (Found: C, 76·05; H, 10·0. Calc. for $C_{29}H_{46}O_4$: C, 75·9; H, 10·1%). $\nu_{max.}$ (in CS_2) 1732, 1249, 1235 (axial acetate), 1080, 1047, 982, 919, 902, and 868 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin). Spectrum in KBr, C.S. No. 182. Wall, Eddy, and Serota (*loc. cit.*) give m. p. 167°, $[\alpha]_D^{25}$ +30°.

cyclo-ψ-Sarsasapogenin on being refluxed with acetic anhydride gave an uncrystallisable gum having an infrared spectrum with the characteristics of that of a ψ-sapogenin diacetate; hydrolysis gave ψ-sarsasapogenin, identified by comparison with an authentic specimen.

cyclo-ψ-neo*Tigogenin*.—Prepared by method (*a*) from ψ-*neo*tigogenin, cyclo-ψ-neo*tigogenin* separated from ethanol in rhomboid plates containing solvent of crystallisation which, after a transition at 140°, melted at 168° and resolidified to needles melting at 186—189°, $[\alpha]_D^{21}$ +25°, $[\alpha]_{5461}^{21}$ +30° (*c*, 0·616) (Found: in substance dried at 130° *in vacuo*: C, 77·4; H, 10·4. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·65%). $\nu_{max.}$ (in CS_2) 3620 and 1038 (equatorial OH), 1362, 1080, 1048, 984, 918, 902, and 868 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin). The spectrum showed similar bands in potassium bromide (C.S. No. 183), a double peak at 1052 and 1045 cm.$^{-1}$ and the equality of the bands at 921 and 902 cm.$^{-1}$ being notable features.

The *acetate* separated from methanol as plates, m. p. 169·5—173°, $[\alpha]_D^{20}$ +11°, $[\alpha]_{5461}^{20}$ +13° (*c*, 0·33) (Found: C, 76·05; H, 10·0. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%). $\nu_{max.}$ (in CS_2) 1731 and 1240 (acetate), 1080, 1048, 985, 916, 900, and 865 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin) (Fig. 3). Spectrum in KBr, C.S. No. 184.

When *cyclo*-ψ-*neo*tigogenin was boiled with acetic anhydride a non-crystalline product was

obtained, having an infrared spectrum with the characteristics of that of a ψ-sapogenin diacetate; hydrolysis gave ψ-*neo*tigogenin, identified by comparison with an authentic specimen.

cyclo-ψ-*Sisalagenin*.—This was prepared by general method (*a*) from ψ-sisalagenin. The value of $[\alpha]_D$ in the ethanol solution changed from +86° to +95° during the reaction. cyclo-ψ-*Sisalagenin* separated from methanol as plates, m. p. 180—184°; another specimen had m. p. 177—182·5° and resolidified to needles, m. p. 192°, $[\alpha]_D^{21}$ +95°, $[\alpha]_{5461}^{21}$ +116° (*c*, 0·758) (Found: C, 74·8, 75·7; H, 9·7, 9·75. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). $\nu_{max.}$ (in CS_2) 1705 (ketone), 3620 and 1038 (equatorial OH), 1362, 1082, 1048, 979, 918, 902, and 868 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin). Spectrum in KBr, C.S. No. 185.

The *acetate* had m. p. 204—208°, $[\alpha]_D^{20}$ +93°, $[\alpha]_{5461}^{20}$ +112° (*c*, 0·405) (Found: C, 73·7; H, 9·2. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). $\nu_{max.}$ (in CS_2) 1735 and 1240 (acetate), 1708 (ketone), 1080, 1049, 980, 916, 901, and 868 cm.$^{-1}$ (*cyclo*-ψ-normal sapogenin). Spectrum in KBr, C.S. No. 186.

Refluxed with acetic anhydride, on one occasion *cyclo*-ψ-sisalagenin yielded the acetate, but on a second ψ-sisalagenin diacetate was obtained. This crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 112—113°, $[\alpha]_D^{22}$ +77°, $[\alpha]_{5461}^{22}$ +94°. $\nu_{max.}$ (in CS_2) 1732 and 1238 (acetate), 1706 (ketone), 1690, and 1028 cm.$^{-1}$ (ψ-sapogenin) (Spectrum in KBr, C.S. No. 187). The substance was identical with material, m. p. and mixed m. p. 112—113°, prepared from ψ-sisalagenin by acetylation with acetic anhydride in pyridine (Callow and James, *loc. cit.*).

Studies of the Equilibrium between ψ- *and* cyclo-ψ-*Sapogenins*.—(i) *Optical rotation*. A 0·565% solution of *cyclo*-ψ-hecogenin in ethanol had $[\alpha]_D^{22}$ +22°, unchanged after 24 hr., but on the addition of 10% by volume of 0·1N-hydrochloric acid in 90% ethanol the specific rotation rose within 15 min. to +32°. Under the same conditions hecogenin showed no mutarotation. The same rotation could be approached from ψ-hecogenin. A 0·328% solution in ethanol had $[\alpha]_D$ +100°; addition of 0·1N-hydrochloric acid (1 ml.) to the solution (18 ml.) caused the rotation to drop to +35·5° in 180 min.; there was no further change in 24 hr.

Similar observations were made with 11-oxo*cyclo*-ψ-tigogenin. A solution of 0·2 g. in a mixture of chloroform (7 ml.) and ethanol (10 ml.) showed $[\alpha]_D$ −24°. Two minutes after the addition of a drop of concentrated hydrochloric acid the solution had $[\alpha]_D$ −17°. In the same concentration an acidified solution of 11-oxo-ψ-tigogenin had $[\alpha]_D$ −15°. Little further change was observed in either case with increase in time or quantity of acid at room temperature. If linear relations are assumed the rotation figures indicate the presence of 92% of *cyclo*-ψ-sapogenin in the equilibrium mixture.

(ii) *Ultraviolet absorption*. An ethanolic solution of 11-oxo*cyclo*-ψ-tigogenin showed negligible absorption at 216 mμ; addition of a trace of hydrochloric acid caused the rapid appearance of a peak at 216 mμ ($E_{1\,cm.}^{1\%}$ 12). 11-Oxo-ψ-tigogenin in ethanol showed $\lambda_{max.}$ 215 mμ ($E_{1\,cm.}^{1\%}$ 115), changed on acidification to $\lambda_{max.}$ 215 mμ ($E_{1\,cm.}^{1\%}$ 13).

Similarly, *cyclo*-ψ-sarsasapogenin in neutral ethanolic solution showed general absorption only at 215 mμ ($E_{1\,cm.}^{1\%}$ 10); on acidification, the solution had $\lambda_{max.}$ 215 mμ ($E_{1\,cm.}^{1\%}$ 25). The corresponding figures for ψ-sarsasapogenin were 215 mμ ($E_{1\,cm.}^{1\%}$ 145) and 207—217 mμ ($E_{1\,cm.}^{1\%}$ 25).

(iii) *Paper-partition chromatography*. Paper chromatography on Whatman No. 2 papers in an acidic solvent (cf. Sannié and Lapin, *Bull. Soc. chim. France*, 1952, 1080) and another containing pyridine shows how the ψ- and *cyclo*-ψ-compounds change in acid circumstances. The *cyclo*-ψ-normal compounds generate the normal sapogenins more quickly than the corresponding *cyclo*-ψ-*iso*-compounds give the *iso*-sapogenins (see footnote to Table 2). The ψ-sapogenins were applied to the paper in pyridine solutions, which were stored at 0°. Unless stated otherwise, the chromatograms were equilibrated for 2 days and then run at 30° ± 1°. The solvents ran downwards. Ethanolic phosphomolybdic acid (10% w/v) (cf. Kritchevsky and Kirk, *Arch. Biochem. Biophys.*, 1952, **35**, 346) or Komarowsky's reagent (cf. Nogare and Mitchell, *Analyt. Chem.*, 1953, **25**, 1376) revealed the sapogenins as lasting blue or yellow spots when the papers were heated gently. Komarowsky's reagent was made for this purpose as follows: A 2% (w/v) solution (10 ml.; if necessary percolated through an alumina pad) of *p*-hydroxybenzaldehyde in ethanol was mixed just before use with concentrated sulphuric acid (0·4 ml.). Papers thus sprayed did not last long. The R_F values are given in Table 2.

Hydrogenation of cyclo-ψ-*Tigogenin*.—Platinum oxide (0·5 g.) was reduced under hydrogen in acetic acid (15 ml.) containing anhydrous sodium acetate (0·1 g.). *cyclo*-ψ-Tigogenin acetate (0·6 g.) in glacial acetic acid (15 ml.) containing anhydrous sodium acetate (0·05 g.) was then added and the hydrogenation continued at 20°/766 mm. The uptake ceased after 30 min. at 34 ml. of hydrogen (1·1 mol.). After filtration the solvent was removed by evaporation and the product was crystallised from methanol, giving needles, m. p. 145—151°. Acetylation with

acetic anhydride in pyridine overnight gave dihydro-ψ-tigogenin diacetate as needles (from methanol), m. p. 123—124°, unchanged by two further recrystallisations. The m. p. of a mixture with dihydro-ψ-tigogenin diacetate (see below) was 123—124°, and of a mixture with dihydrotigogenin diacetate (m. p. 114—116°) was 110—114°. $[\alpha]_D^{20}$ was −17° (*c*, 0·65) (Found: C, 74·2; H, 9·9. Calc. for $C_{31}H_{50}O_5$: C, 74·1; H, 10·0%). $\nu_{max.}$ (in CS_2): 1734, 1236 (acetate), and 1020 cm.$^{-1}$. There was no vinyl ether band at 1690 cm.$^{-1}$. No appreciable absorption in

TABLE 2.

Parent sapogenin	Solvent: pyridine (8); light petroleum, b. p. 100—120° (15); water (3)			Solvent: light petroleum (100); chloroform (10); acetic acid (1)		
	Named form	*cyclo*-ψ-	ψ-	Named form	*cyclo*-ψ-	ψ-
Tigogenin	0·95	0·90	0·50	0·82	0·82, 0·30	0·80, 0·30
*neo*Tigogenin ...	0·95	0·87	0·48	0·80	0·80	0·80, 0·25 *
Sarsasapogenin	0·95	0·95	0·61	0·89	0·90	0·85, 0·41 *
Smilagenin	0·95	0·95	—	0·89	0·89	—
Hecogenin	0·71	0·69	0·07	0·40	0·40	0·38, 0·06 *
Sisalagenin	0·73	0·72	0·07	0·50	0·50, 0·33	0·50, 0·35, 0·06 *
11-Oxotigogenin	0·76	0·76	0·09	0·62	0·46, 0·12	0·46, 0·10

* These fractions were detectable only if the equilibration was omitted, so that exposure to the acid-containing solvent lasted only for the time of development (*ca.* 1·5 hr.).

the ultraviolet was found above 200 mμ. The compound gave no colour with tetranitromethane.

Dihydro-ψ-tigogenin diacetate slowly decolorised a solution of bromine in acetic acid; dihydrotigogenin diacetate failed to react under these conditions (cf. Marker, Jones, and Krueger, *J. Amer. Chem. Soc.*, 1940, **62**, 2532).

Hydrogenation of ψ-Tigogenin.—ψ-Tigogenin (1·0 g.) was hydrogenated as described for the *cyclo*-ψ-compound, but with twice the quantity of acetic acid; the theoretical volume of hydrogen was taken up in 11 min. The product was acetylated with pyridine and acetic anhydride at 100° for 30 min. The product, after crystallisation from methanol, had m. p. 123—124°, unchanged by further crystallisation, and $[\alpha]_D^{20}$ −15·5° (*c*, 0·775). Marker *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 3003; 1947, **69**, 2167) give m. p. 122—124°.

Hydrogenation of Tigogenin Acetate.—Tigogenin acetate (2·0 g.) was hydrogenated as described for the *cyclo*-ψ-compound. Uptake of hydrogen was extremely slow and some 60 hr. were required for completion of the reduction. Acetylation with pyridine–acetic anhydride at 100° for 30 min. gave dihydrotigogenin diacetate (2·0 g.) with m. p. 114—116°, unchanged by further crystallisation from methanol, and $[\alpha]_D^{20}$ −12·5° (*c*, 0·91). Doukas and Fontaine (*J. Amer. Chem. Soc.*, 1953, **75**, 5355) give m. p. 116—117° and $[\alpha]_D^{20}$ −15°.

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GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX.
NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
THE RIDGEWAY, MILL HILL, N.W.7.

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Kinetic Studies on the Dealkylation of Esters of Phosphorous, Phosphoric, and Phosphonic Acid. Part I. Dealkylation by Hydrogen Bromide in Ether.

By V. F. G. Cooke and W. Gerrard.

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The kinetics of the dealkylation of diethyl hydrogen phosphite, triethyl phosphate, an acetylphosphonate, and alkylphosphonates by hydrogen bromide in ether have been measured. They are consistent with replacement of the first and the second alkyl group by successive reactions each of the second order with respect to the reactants. The rate constants have been evaluated, and provide quantitative measures of the variation in rate with variation of the alkyl groups R and R′ in phosphonates, O:PR(OR′)$_2$; they indicate the degree of control available in the preparation of esters of the type O:PR(OR′)·OH, O:PH(OR′)·OH, and O:P(OR′)$_2$·OH.

An important feature of alkyl phosphites, phosphates, and phosphonates is their dealkylation by hydrogen halides, which remove alkyl groups as alkyl halide. Qualitative studies have previously been made by Gerrard (*J.*, **1940**, **1464**; **1944**, **85**; **1945**, **848**), Cooke, Gerrard, and Green (*Chem. and Ind.*, **1953**, **351**), Gerrard, Green, and Nutkins (*J.*, **1952**, **4076**), and Gerrard, Isaacs, Machell, Smith, and Wyvill (*J.*, **1953**, **1920**), and kinetic studies were initiated by Gerrard and Whitbread (*J.*, **1952**, **914**) who showed that the rates of successive removal of alkyl groups from tri-*n*-butyl phosphite were in the order 1st $\gg$ 2nd $>$ 3rd, for a given hydrogen halide, and that for each group the rates were in the order HI $>$ HBr $>$ HCl.

The measurements of rates of dealkylation of a number of esters of the type O:PR′(OR)$_2$ were undertaken to generalise the kinetic technique for such consecutive reactions, to elucidate mechanisms of dealkylation, to indicate conditions for the preparation of acid esters, and to reveal to what extent electronic influence is transmitted through the phosphorus atom.

Rate measurements reveal that the main reactions studied are (*a*) and (*b*). These are competitive consecutive reactions in which the material measured is consumed in each.

(*a*) O:PR′(OR)$_2$ + HBr ⟶ O:PR′(OR)·OH + RBr

(*b*) O:PR′(OR)·OH + HBr ⟶ O:PR′(OH)$_2$ + RBr

A strict mathematical solution of general applicability has not yet been devised. Frost and Schwemer (*J. Amer. Chem. Soc.*, **1952**, **74**, **1268**), however, provided an analysis for the case where the reactants are stoicheiometrically equivalent. Their purpose was to integrate this kinetic system in terms of general variables which could be applied to experimental results for this class of reaction, and they tested their procedure on the hydrolysis of ethyl adipate and succinate. When the ratio of the rate constants k_1/k_2 is more than 10 the following method is easier and is not restricted to equimolecular concentrations.

Evaluation of Specific Rate Constants, k_1 and k_2.—When $k_1 > 10k_2$, let a_0 be the initial concentration of hydrogen bromide, b_0 be the initial concentration of the ester, a and b the concentration at time t, and c the concentration of the half ester, then

$$-da/dt = k_1ab + k_2ac \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

When $k_1 > 10k_2$, for a measurable initial extent of reaction, the approximate equation (2) holds sufficiently accurately to allow evaluation of k_1:

$$-da/dt = k_1ab \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

by the usual integrated expression for such a second-order equation. For the later stages of reaction, the following approximate equation becomes progressively more applicable:

$$-da/dt = k_2ac$$

If a' is the hydrogen bromide consumed by the first dealkylation and a'' that by the second in time t, then

$$a = a_0 - a' - a'' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and at later stages $a' \approx b_0$.

Hence

$$-da/dt = k_2 a(a' - a'')$$
$$= k_2 a(2b_0 - a_0 + a) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

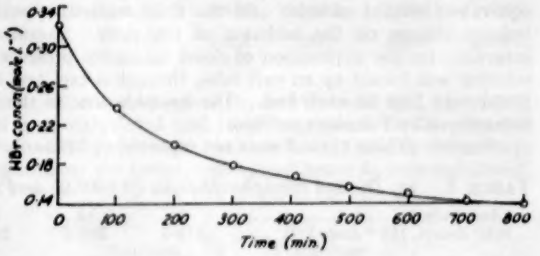
Integrating, we have :

$$\frac{1}{2b_0 - a_0} \log \left(\frac{2b_0 - a_0 + a}{a} \cdot \frac{a_0}{2b_0} \right) = k_2 t \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

For the special case of initially equimolecular concentrations $a_0 = 2b_0$, we have

$$1/a - 1/a_0 = k_2 t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

It is also possible to extend Frost and Schwemer's tables (*loc. cit.*) for cases where $k_1 > 10k_2$. This laborious procedure was performed and compared for typical cases with the method given above. The equality of results demonstrated the reliability of the methods.



Comparison of calculated and experimental curves for the hydrolysis of diethyl ethylphosphonate by ethereal hydrogen bromide.

— Calculated curve.
○ Points read from experimental curve.

The middle part of the reaction curve was not used in evaluation of rate constants when $k_1/k_2 > 10$. It is worth investigating if the values of k_1 and k_2 do supply a calculated rate in this region in agreement with experiment. This can be done by utilising Frost and Schwemer's equation (7) :

$$\tau = \frac{1 - \kappa}{1 - 2\kappa} \int_{\beta}^{1} \frac{d\beta}{\beta^2[1 + \beta^{\kappa-1}/(1 - 2\kappa)]} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $\beta = b/b_0$, $\kappa = k_2/k_1$ and $\tau = b_0 k_1 t$. For κ determined from initial and final stages, graphical integration of (7) for various values of β was performed to give corresponding values of τ. For each value of β, the value of $\alpha = a/a_0$ was found by Frost and Schwemer's equation (10) :

$$\alpha = [(1 - 2\kappa)/2(1 - \kappa)]\beta + [1/2(1 - \kappa)]\beta^{\kappa}$$

Hence, since α and τ are known, a calculated line of α *versus* t could be drawn for appropriate values of a_0. The fit was very satisfactory (see Figure).

Frost and Schwemer's analysis was devised to obtain rate constants for cases where $k_1 < 10k_2$. The times required to reach specified extents of reaction are measured, and several ratios taken, *e.g.*, the times required for 60% and for 30% reaction. These ratios are obviously dependent on the relative values of k_1 and k_2. Tables are provided for using these ratios and absolute times of reaction so as enable k_1 and k_2 to be read off. For various ratios, with one initial equimolecular concentration and for various initial equimolecular concentrations, constant values for k_1 and k_2 were obtained for the stepwise dealkylations mentioned.

Experimental

Preparation of Esters.—Dialkyl alkylphosphonates were prepared from the corresponding trialkyl phosphites and an alkyl halide, by the Arbuzov reaction (*J. Russ. Phys. Chem. Soc.*, **1906**, **38**, 687) and were purified by careful fractionation. Diethyl ethylphosphonate had b. p. 82°/10 mm., n_D^{20} 1·4168 (Found : P, 18·75. Calc. for $C_6H_{15}O_3P$: P, 18·7%). Diethyl *n*-octylphosphonate had b. p. 83°/0·02 mm., n_D^{18} 1·4353 (Found : P, 12·4. Calc. for $C_{12}H_{27}O_3P$: P,

12·4%). Diethyl 1-phenylethylphosphonate (prepared as described by Gerrard and Green, *loc. cit.*) had b. p. 88°/0·05 mm., n_D^{18} 1·4870 (Found: P, 12·7. Calc. for $C_{12}H_{19}O_3P$: P, 12·8%). *Di-n-propyl ethylphosphonate* had b. p. 112°/15 mm., n_D^{20} 1·4238 (Found: C, 49·5; H, 9·80; P, 16·0. $C_8H_{19}O_3P$ requires C, 49·5; H, 9·85; P, 15·95%). *Diisopropyl ethylphosphonate* had b.p. 90°/19 mm., n_D^{20} 1·4122 (Found: P, 16·1. $C_8H_{19}O_3P$ requires P, 15·95%). Diethyl acetylphosphonate, b. p. 110°/17 mm., n_D^{17} 1·4240 (Found: P, 17·25. Calc. for $C_6H_{13}O_4P$: P, 17·2%), was prepared by Kabachnik and Rossiiskaya's method (*Isvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 1945, 364), but our yield of 78% was considerably better than theirs. Diethyl hydrogen phosphite, b. p. 82°/18 mm., n_D^{18} 1·4100 (Found: P, 22·6. Calc. for $C_4H_{11}O_3P$: P, 22·45%), was prepared as described by Gerrard (*J.*, 1940, 1464). Triethyl phosphate had b. p. 102—103°/15 mm., n_D^{20} 1·4061 (Found: P, 17·0. Calc. for $C_6H_{15}O_4P$: P, 17·0%).

The solvent used in the kinetic runs was the best grade of ether, and was distilled from sodium before use.

Method and Appartus.—Hydrogen bromide and the phosphonate in ethereal solution were allowed to react in a thermostat. A solution of hydrogen bromide was first prepared by passing the dry gas into the ether, and the approximate concentration of the solution was determined. This stock solution was then diluted with more solvent, to a known volume, to give approximately the concentration required, and its exact molarity determined. The stoicheiometrically equivalent weight of ester and the final molarities were calculated, after allowance for the volume change on the addition of the ester. Samples were removed after specified time intervals, by the application of dried air under pressure to the surface of the solution. The solution was forced up an exit tube, through a tap, and into a sampler of known volume, also fitted with taps at each end. The bromide ion, in the aqueous extract of each sample, was determined by Volhard's method.

Results.—Three typical runs are reported in Tables 1, 4, and 6.

TABLE 1. (a) *Diethyl ethylphosphonate* (0·1605M) *and hydrogen bromide* (0·3205M) *at* 25·0°.

Time (min.)	2	15	30	60	100	180
HBr concn. (10^{-3} mole $l.^{-1}$)	318·5	302·5	283·5	261	238	206·5
Time (min.	245	320	408	1360	1682	2757
HBr concn. (10^{-3} mole $l.^{-1}$)	190	176·5	166	118	112	96
Time (min.)	4290	6075	8360	9840		
HBr concn. (10^{-3} mole $l.^{-1}$)	76	63	49·5	46		

(*a*) (See Table 1.) From the smooth curve drawn on a large scale through the experimental points, the hydrogen bromide concentrations at equal intervals of time were read for the first half of the complete reaction. The corresponding ester concentrations were calculated, neglecting the second reaction, and a graph of log ([HBr]/[Ester]) *versus* time was plotted. The data in Table 2 were thus used.

TABLE 2.

Time (min.)	0	20	40	60	80	100	120
log ([HBr]/[Ester])	0·300	0·339	0·378	0·412	0·448	0·485	0·521
Time (min.)	140	160	180	220	260	300	340
log ([HBr]/[Ester])	0·559	0·601	0·646	0·741	0·843	0·958	1·094

From the initially linear slope, k_1 (the second-order specific rate for the first dealkylation) was calculated to be $4{\cdot}43 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. A curve of hydrogen bromide concentration *versus* time was also drawn for the whole reaction, and hydrogen bromide concentrations at larger time intervals read off. A graph of log 1/[HBr] *versus* time was plotted (see Table 3).

TABLE 3.

Time (min.)	500	1000	2000	3000	4000	5000	6000	7000	8000	9000
1/[HBr] (l. mole^{-1})	6·33	7·69	9·40	11·0	12·7	14·3	15·9	17·5	19·4	20·8

TABLE 4. (b) *Diethyl* n-*octylphosphonate* (0·0730M) *and hydrogen bromide* (0·1460M) *at* 25·0°.

Time (min.)	3	16	40	86	147	206	250	305	380	460
HBr concn. (10^{-3} mole $l.^{-1}$)	145	140·5	133	122	115	107·5	104	100	95	91
Time (min.)	1182	1408	1825	3085	5850	8630	14,620	20,150	24,750	
HBr concn. (10^{-3} mole $l.^{-1}$)	72·5	70·5	67	59·5	51·5	45	39	33	31	

The slope of the linear part of this curve was equal to k_2 (the second-order specific rate for the second dealkylation) = $2{\cdot}65 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. The ratio k_1/k_2 was thus 16·7.

TABLE 5.

Time (min.)	0	20	60	100	140	180	220	260	300
log ([HBr]/[Ester])...	0·301	0·325	0·365	0·401	0·433	0·468	0·503	0·536	0·570
Time (min.)	340	380	420	460					
log ([HBr]/[Ester])...	0·603	0·637	0·670	0·698					
Time (min.)	2000	4000	6000	8000	10,000	12,000	14,000	18,000	22,000
1/[HBr] (l. mole^{-1})...	15·2	17·7	19·4	20·8	22·2	23·6	25·0	28·2	30·8

(*b*) (See Table 4.) Graphs of log [HBr]/[Ester] and 1/[HBr] *versus* time were plotted as before, with the results given in Table 5. The value of k_1 was $4{\cdot}45 \times 10^{-4}$ and of k_2 $1{\cdot}22 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. The ratio k_1/k_2 in this case was 36·5, and hence the deviation from linearity of the log [HBr]/[Ester] plot develops much later.

TABLE 6. (c) *Diethyl acetylphosphonate* (0·1095M) *and hydrogen bromide* (0·2180M) *at* 25·0°.

Time (min.)	2	17	30	69	131	197	275	351
$a = [HBr]/[HBr]_0$ ...	0·996	0·985	0·969	0·940	0·892	0·849	0·792	0·732
Time (min.)	445	504	1400	1715	2025	2810	4290	5970
$a = [HBr]/[HBr]_0$ ...	0·691	0·678	0·429	0·383	0·346	0·275	0·188	0·141

(*c*) (See Table 6.) a *versus* time was plotted on a large scale, and times of 20% up to 60% reaction were read. The "t" ratios were calculated and by interpolation in the prepared tables of Frost and Schwemer the corresponding values of $1/\kappa$ were found. From the average $1/\kappa$ value, the values of τ were also found from the tables, and k_1 and hence k_2 were calculated. Results are in Tables 7 and 8.

TABLE 7.

Reaction (%)	t (min.)	Percentage compared	"t" ratio	$1/\kappa$	Reaction (%)	t (min.)	Percentage compared	"t" ratio	$1/\kappa$
20	265	60/20	6·038	2·046	50	1062	60/50	1·506	2·092
30	450	60/30	3·556	2·145	60	1600	50/20	4·012	2·030
40	715	60/40	2·248	2·000			50/30	2·363	2·181

Average $1/\kappa$ = 2·08

TABLE 8.

Reaction (%)	20	30	40	50	60
τ	0·2510	0·4311	0·6727	1·012	1·523
$10^{-4}k_1$ (l. mole^{-1} sec.$^{-1}$)	1·446	1·462	1·436	1·453	1·453

Average $k_1 = 1{\cdot}45 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.
Average $k_2 = 1{\cdot}45 \times 10^{-4}/2{\cdot}08 = 6{\cdot}97 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

The rate constants obtained for the various esters, in ethereal solution, are summarised in Table 9.

TABLE 9.

Ester	Initial concn. (mole l.$^{-1}$) HBr	Ester	Rate constants (l. mole^{-1} sec.$^{-1}$) 10^4k_1	10^5k_2	k_1/k_2 *
Et·PO_2Et_2	0·3205, 0·1485	0·1605, 0·0750	4·43, 4·27	2·65, 2·50	17·2
	0·1880, 0·0710	0·0940, 0·0355	4·26, 4·33	2·35, 2·64	
Et_2HPO_2	0·3945, 0·2400	0·1970, 0·1200	4·73, 4·45	3·44, 3·50	13·1
n-C_8H_{17}·PO_2Et_2	0·1340, 0·1460	0·0670, 0·0730	4·30, 4·45	1·31, 1·22	34
CHPhMe·PO_2Et_2	0·2070, 0·1270	0·1070, 0·0635	3·37, 3·07	1·38, 1·33	23
Ac·PO_2Et_2	0·1960, 0·2180	0·0980, 0·1095	1·37, 1·45	6·56, 6·97	2·1
Et·$PO_2Pr^n_2$	0·3045, 0·1895	0·1525, 0·0950	3·56, 3·78	1·23, 1·31	28
Et·$PO_2Pr^i_2$	0·2200, 0·1380	0·1105, 0·0690	0·933, 0·986	0·880, 0·917	10·7
Et_3PO_4	0·1710	0·0855	9·02	7·13	12·7
Et_2HPO_2 at 15·0°	0·1575, 0·1540	0·0785, 0·0775	0·921, 0·924	1·72, 1·73	5·4
Et·PO_2Et_2 at 15·0°	0·1767	0·0825	1·38	0·68	20·3
Et_3PO_4 at 15·0°	0·3130	0·1040	3·12	3·06	10·2
Et_2HPO_2 at 20·0°	0·1100	0·0660	1·95	—	—

* From average values of k_1 and k_2.

Discussion

In each example the dealkylation was clearly of the second order; but because the observations were all for ethereal solutions, and the influence of ether has not yet been decided, a detailed discussion on mechanism must be postponed until data for other solvents and conditions are available. It is possible that, even if competitive complex-formation between hydrogen bromide and ether did not complicate the kinetics, it might still affect the values of the rate constants. Ether was chosen because of the convenient solubility of hydrogen bromide. Nevertheless the results provide a quantitative comparison of the influence of structure on the first and the second dealkylation, and also clearly show the degree of control which may be held over the steps of dealkylation.

Replacement of hydrogen by an ethyl or *n*-octyl group in the compound $O{:}PH(OEt)_2$ has little effect on k_1 (the first dealkylation), but has more effect on k_2 (the second one), and increases the ratio k_1/k_2. Thus for diethyl hydrogen phosphite k_1/k_2 is 13·1, for diethyl ethylphosphonate 17·2, and for diethyl *n*-octylphosphonate 34. These ratios indicate to what extent dealkylation may be restricted to the first group, and so lead to the convenient preparation of the acid esters. Ethyl hydrogen *n*-octylphosphonate, $O{:}PR(OEt)(OH)$, was obtained in this way by Cooke, Gerrard, and Green (*Chem. and Ind.*, 1953, 351). In view of the great reactivity of the 1-carbon atom in 1-phenylethanol (cf. Gerrard, *J.*, 1944, 88; Gerrard and Shepherd, *J.*, 1953, 2069), the difference between k_1 ($3{\cdot}2 \times 10^{-4}$) for diethyl 1-phenylethylphosphonate and k_1 ($4{\cdot}3 \times 10^{-4}$) for diethyl hydrogen phosphite appears surprisingly small. The acetyl group has a more marked effect: $k_1 = 1{\cdot}4 \times 10^{-4}$, but k_2 is larger than for the hydrogen phosphite, making $k_1/k_2 = 2$. For such an ester, the production of the acid ester will be very much less efficient.

Replacement of the ester ethyl group by *n*-propyl, $O{:}PEt(OEt)_2 \longrightarrow O{:}PEt(OPr^n)_2$, caused a slight reduction in k_1, and a greater one in k_2, thus increasing the ratio k_1/k_2 to 28. Replacement by *iso*propyl, to give $O{:}PEt(OPr^i)_2$, causes a considerable reduction in k_1 ($0{\cdot}96 \times 10^{-4}$), but a smaller reduction in k_2, lowering the ratio k_1/k_2 to 11.

For triethyl phosphate, k_1 and k_2 are both twice as large as for diethyl hydrogen phosphite. This could be due in some measure to the statistical availability of alkyl groups.

In the types of ester studied, the phosphorus atom is quinquevalent and of the general structure $O{:}PX(OR)_2$, where X = H, OR, or R, or R′; but a trialkyl phosphite, $P(OR)_3$, contains a tervalent phosphorus atom, and the much greater rate of the first dealkylation, $P(OR)_3 + HBr \longrightarrow O{:}PH(OR)_2 + RBr$, may be partly attributed to a tendency for phosphorus to attain quinquecovalency. It was found by Gerrard and Whitbread (*loc. cit.*) that, in 0·2M-concentration and with hydrogen bromide, tri-*n*-butyl phosphite was completely dealkylated to dibutyl hydrogen phosphite in 7 minutes at −11°. Of relevance is the fact that in the examples of alcohols of ordinary reactivity it is the dialkyl hydrogen phosphite, and never the trialkyl phosphite, which can be obtained by the interaction of the alcohol and phosphorus trichloride.

We thank Dr. W. F. Watson for helpful discussions.

The Northern Polytechnic,
Holloway Road, London, N.7.

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*Cafestol. Part I.**

By R. D. Haworth, A. H. Jubb, and J. McKenna.

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The molecular composition of cafestol, $C_{20}H_{28}O_3$, has been confirmed by the *X*-ray method, and the compound is shown to be pentacyclic. Suggestions by previous workers of presence of the $>C(OH)\cdot CH_2\cdot OH$ group in a five-membered carbocyclic ring, and of a 2 : 3-disubstituted furan nucleus attached to a six-membered carbocyclic ring have also been confirmed. A new series of degradation products is described and some partial structures are considered, but the complete structure of the framework is not yet known.

Cafestol, $C_{20}H_{28}O_3$, is the main constituent of the non-saponifiable part of coffee-bean oil, and early attempts at purification (Noël and Dannmeyer, *Strahlentherapie*, 1929, **32**, 769; 1930, **38**, 583; Bengis and Anderson, *J. Biol. Chem.*, 1932, **97**, 99; Prescott, Emerson, Woodward, and Heggie, *Food Res.*, 1937, **2**, 165; Sabalitschka and Schüching, *Apoth. Ztg.*, 1938, **53**, 760; Wagner, *Z. Unters. Lebensm.*, 1939, **77**, 225; Slotta and Neisser, *Ber.*, 1938, **71**, 1991) were rendered difficult by presence of a more unsaturated substance known as kahweol, which was sensitive to oxygen, light, heat, and mineral acids and was responsible for the development of a yellow colour, the lowering in melting point, the increase in negative optical rotation on storage, and for the band in the ultraviolet spectrum at 2900 Å. The reported œstrogenic activity (Slotta and Neisser, *loc. cit.*) led to extensive structural investigations by the same authors (*Ber.*, 1938, **71**, 2342), Hauptmann and Franca (*Z. physiol Chem.*, 1939, **259**, 245; *J. Amer. Chem. Soc.*, 1943, **65**, 81), Wettstein, Fritzsche, Hunziker, and Miescher (*Helv. Chim. Acta*, 1941, **24**, 332 E), Wettstein and Miescher (*ibid.*, 1943, **26**, 631), Wettstein, Hunziker, and Miescher (*ibid.*, p. 1197), Wettstein, Spillmann, and Miescher (*ibid.*, 1945, **28**, 1004), Chakravorty, Levin, and Wesner (*J. Amer. Chem. Soc.*, 1943, **65**, 929), and Chakravorty, Levin, Wesner, and Reed (*ibid.*, p. 1325).

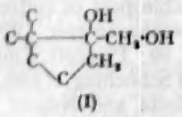
The early steroid structure suggested by Slotta and Neisser (*loc. cit.*, p. 2342) was abandoned when the œstrogenic inactivity of cafestol was established (Bauer and Neu, *Fette u. Seifen*, 1942, **49**, 419; Wettstein *et al.*, *loc. cit.*, 1941; Hauptmann and Franca, *loc. cit.*), and a structure of diterpenoid type came into favour. Cafestol was shown to contain a primary and a tertiary hydroxyl group (Slotta and Neisser, *loc. cit.*), which Hauptmann and Franca (*loc. cit.*) showed were present in an α-glycol structure, $>C(OH)\cdot CH_2\cdot OH$, yielding the aldehyde $-CH\cdot CHO$ when cafestol or its acetate was distilled with zinc dust; the tertiary hydroxyl group could also be eliminated with boiling acetic anhydride. Hydrogenation, as well as oxidation with per-acids, indicated presence of two double bonds, which were conjugated as proved by formation of an adduct with maleic anhydride (Wettstein *et al.*, *loc. cit.*, 1941). Wettstein *et al.* also oxidised cafestol with lead tetra-acetate; the glycol groupings was attacked with the formation of epoxynorcafestadienone, $C_{19}H_{24}O_2$, which was shown to be a *cyclo*pentanone as oxidation of the ketone (epoxynorcafestanone-A), similarly derived from tetrahydrocafestol, with potassium hypoiodite gave a dicarboxylic acid, $C_{19}H_{28}O_5$, yielding an anhydride. As the dibasic acid contained one hindered carboxyl group (methyl ester resistant to hydrolysis) which is probably † tertiary, the glycol grouping in cafestol may be present as partial structure (I) or (II). Although earlier workers failed, by treatment with *m*-nitrobenzaldehyde, to provide evidence for the ketomethylene group in epoxynorcafestadienone, Djerassi, Wilfred, Visco, and Lemin (*J. Org. Chem.*, 1953, **18**, 1449), during the course of our experiments, have established this by condensation with ethyl formate to a hydroxymethylene-ketone. They also confirmed the presence of the five-membered ring by infrared measurements on epoxynorcafestadienone (band at 1742 cm.$^{-1}$).

The nature of the third oxygen atom in cafestol has been the subject of several communications but contrary to earlier suggestions [Fieser and Fieser, "Natural Products

* A preliminary account of this work was published in *Chem. and Ind.*, 1954, 104.

† But not of course conclusively so: the carboxyl group might also, for example, be secondary but subject to considerable steric hindrance. A similar ambiguity exists concerning one of the carboxyl groups formed in the oxidative fission of the six-membered ring adjacent to the furan ring (see p. 1984).

related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 80; Ferrari, *Il Farmaco* (*Pavia*), 1950, **5**, 47; 1951, **6**, 726; 1952, **7**, 3] the infrared spectrum shows absence of bands in the carbonyl region. Wettstein and Miescher (*loc. cit.*) put forward the concept of a 2 : 3-disubstituted furan ring (III) to explain the sensitivity to acids and the behaviour on oxidation and reduction. The furan ring is remote from the glycol grouping because Hauptmann and Franca (*loc. cit.*) showed by ultraviolet measurements that, when the tertiary hydroxyl group was removed by dehydration, the newly formed double bond is not conjugated with the original double bond system, and the carbonyl group of epoxynorcafestadienone is not in conjugation with the furan chromophore. Wettstein, Hunziker, and Miescher (*loc. cit.*) explained the reaction of per-acids with cafestol acetate on the basis of the conversion of the furan ring (III) into the hydroxy-lactone structure (IV). Again, the attachment of the furan ring to the remainder of the molecule was suggested by the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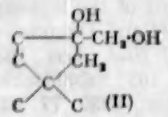
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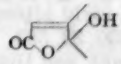
(III)

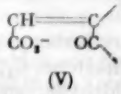

(IV)

ozonisation of epoxynorcafestadienone to a keto-dicarboxylic acid, $C_{17}H_{24}O_5$, derived by rupture of the furan ring and loss of two mols. of carbon dioxide. This keto-dicarboxylic acid gave on pyrolysis a diketone, $C_{16}H_{22}O_2$, and consequently Wettstein, Hunziker, and Miescher (*loc. cit.*) deduced that the ring adjoining the furan ring was six- or seven-membered. It was also shown that the keto-dibasic acid probably contained one tertiary carboxyl group and that the diketone, $C_{16}H_{22}O_2$, condensed with *m*-nitrobenzaldehyde; in view of the failure of epoxynorcafestadienone to condense with *m*-nitrobenzaldehyde (see above) this evidence indicates presence of a ketomethylene group in the ring formed by pyrolysis of the keto-dicarboxylic acid, $C_{17}H_{24}O_5$. The oxidation of the maleic anhydride adduct of cafestol acetate to mellophanic acid suggested that the furan ring was attached to the rest of the molecule by the 2 : 3-carbon atoms. Djerassi and his co-workers (*loc. cit.*) have confirmed these views by measurements of the infrared spectrum of the diketone, $C_{16}H_{22}O_2$, which showed carbonyl bands at 1744 and 1737 cm.$^{-1}$ and consequently the presence of two *cyclo*pentanone rings.

Our researches have overlapped to a certain extent with those of Djerassi and his co-workers, and our results confirm their findings. The isolation of pure cafestol from Santos coffee beans, Jamaica coffee beans, and coffee oil or residues kindly supplied by Messrs. J. Lyons and Company Limited is described in the Experimental section; we prefer partial hydrogenation for the elimination of kahweol from crude cafestol as this gives a product without the absorption band at 2900 Å, whereas it is evident from the ultraviolet data that the sodium and alcohol method used by Djerassi and his colleagues and by earlier workers is more tedious. Oxidation of cafestol to epoxynorcafestadienone was carried out with lead tetra-acetate as described by previous workers, and the ketone was readily reduced by hydrazine and potassium hydroxide in diethylene glycol to epoxynorcafestadiene. The new diene retained the furan ring and consequently gave a maleic anhydride adduct, and was reduced to a tetrahydro-derivative, epoxynorcafestane, by hydrogen in presence of palladium–charcoal. On ozonisation epoxynorcafestadiene gave a neutral product of unknown structure and a dibasic acid, $C_{18}H_{34}(CO_2H)_2$, m. p. 149—151°, which gave a cyclic ketone. The infrared spectrum of this ketone indicated a *cyclo*pentanone structure (band at 1740 cm.$^{-1}$) and consequently the dibasic acid was an adipic acid derived from a *cyclo*hexane precursor. These experiments therefore confirm that the ring attached to the furan nucleus is six-membered, and further evidence for this is presented below.

Monoperphthalic acid reacted with epoxynorcafestadiene to give hydroxynorcafestenolide, which contained partial structure (IV), the oxidation being analogous to the conversion of epoxynorcafestadienone into hydroxyoxonorcafestenolide, the acetyl derivative of which was described by Wettstein, Hunziker, and Miescher (*loc. cit.*). Partial structure (IV) has been supported by infrared and ultraviolet measurement, the latter in alkaline solution showing presence of the anion (V). Hydroxynorcafestenolide gave a crystalline

acetyl derivative, a cyclic compound of probable partial structure (VI) with *p*-tolylhydrazine, an anhydro-derivative (VII) when heated with potassium hydrogen sulphate, and the dibasic acid, $C_{15}H_{24}(CO_2H)_2$, m. p. 149—151°, on oxidation with permanganate. We have found that hydroxyoxonorcafestenolide may be prepared directly from cafestol by oxidation with chromic acid, a reagent which gives a similar result with menthofuran (VIII) (Wood-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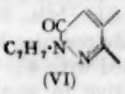
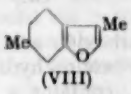
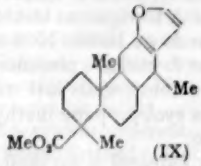

(VI)

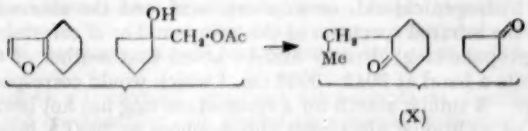
(VII)


(VIII)

ward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399). The ketone was obtained in a crystalline form and gave an acetyl derivative, m. p. 235°, described previously by Wettstein, Hunziker, and Miescher (*loc. cit.*), and dehydration with potassium hydrogen sulphate gave an anhydro-derivative. Oxidation of epoxynorcafestadiene with chromic acid also gave hydroxynorcafestenolide and the above dibasic acid, m. p. 149—151°. The observation by Wettstein, Hunziker, and Miescher (*loc. cit.*) that cafestol acetate was oxidised by monoperphthalic acid, yielding (after further acetylation) diacetoxyhydroxycafestenolide, has been confirmed and we have hydrolysed the product to trihydroxycafestenolide.

In addition, the similarity of the infrared and ultraviolet absorption spectra of cafestol and its derivatives to those of authentic furans, particularly the 2 : 3-disubstituted methyl vinhaticoate (IX) (King and his co-workers, *J.*, 1953, 1055, 4158), leaves no doubt of presence of a furan ring in cafestol. Cafestol exhibits three bands in the infrared region characteristic of C=C stretching; these bands, at 1504 (strong), 1631 (weak), and 1563 cm.$^{-1}$ (very weak), are all absent from the spectrum of tetrahydrocafestol. Methyl vinhaticoate exhibits similar bands at 1506, 1638, and 1563 cm.$^{-1}$ which also disappear on hydrogenation of the furan ring. Differently substituted furans exhibit bands in the same region but not at identical positions: menthofuran (VIII) has strong bands at 1567 and 1642 cm.$^{-1}$ and a weak band at 1770 cm.$^{-1}$, whilst furfuryl alcohol absorbs at 1590 cm.$^{-1}$ (Rogers and Williams, *J. Amer. Chem. Soc.*, 1938, **60**, 2619) and furan at 1580 cm.$^{-1}$ (Pickett, *J. Phys. Chem.*, 1942, **10**, 660). The close similarity in ultraviolet absorption spectra of cafestol, menthofuran, and methyl vinhaticoate ($\lambda_{max.}$ 2220 Å in each case; log ε 3·80, 3·78, and 3·88 respectively) is also noteworthy.


(IX)

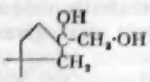

(X)

At an early stage in our experiments repeated unsuccessful attempts were made to prepare cafestol derivatives in which the furan ring had been opened by hydrogenolysis (cf. Wettstein, Fritzsche, Hunziker, and Miescher, *loc. cit.*), but as we could not improve the yields reported by the Swiss workers this approach was abandoned. Our results, which confirm and extend the earlier work, are reported in the Experimental section; it may be noted here that direct proof of hydrogenolysis was afforded by isolation of a triol diacetate, $C_{24}H_{38}O_5$, and additional evidence for presence of a six-membered ring adjoining the furan ring was provided by the infrared absorption spectrum of norcafestanedione (X), derived from cafestol acetate by hydrogenolysis, hydrolysis, and oxidation with chromic acid; the diketone (X) exhibited bands at 1740 (*cyclo*pentanone) and 1706 cm.$^{-1}$ (*cyclo*hexanone). The monoketone (epoxynorcafestanone A) derived from cafestol by hydrogenation of the furan ring and oxidative fission of the glycol group yielded a tribromo-derivative on exhaustive bromination, indicating presence of three hydrogen atoms in the α-position to the *cyclo*pentanone carbonyl group.

We believe the evidence now favours presence in cafestol of (1) the 2 : 3-disubstituted furan type (XI) and (2) the five-membered ring glycol of type (XII). The furan structure

(XI) is required to explain the following features. (*a*) At least one hydrogen atom must be present at 1′ to account for the formation of anhydro-derivatives of type (VII). (*b*) The

(XI)



(XII)

keto-dicarboxylic acid, $C_{17}H_{24}O_5$ (p. 1984), probably contains one tertiary carboxyl group, in which case no hydrogen atoms can be associated with 4′. (*c*) The diketone, $C_{16}H_{22}O_2$ (p. 1984), contains a ketomethylene group reactive to *m*-nitrobenzaldehyde, and two hydrogen atoms must therefore be present at 1′. The structure of type (XII) is necessary to explain (*a*) the conversion into epoxynorcafestadienone which contains a (hindered) ketomethylene group, (*b*) the probable tertiary nature of one carboxyl group in the dibasic acid, $C_{19}H_{28}O_5$ (p. 1983), and (*c*) the production of a tribromo-derivative from epoxynorcafestanone A (p. 1985).

On the other hand the hydrocarbon skeleton of cafestol is quite unknown and in spite of numerous experiments we have failed to isolate recognisable dehydrogenation products by the action of selenium on cafestol or the anhydro-lactones of type (VII); in fact an examination of the ultraviolet spectra of the oily products suggested that little aromatisation had been effected during reaction with selenium. Further attempted dehydrogenation experiments are in progress.

The analytical data for cafestol and its derivatives are, without exception, in agreement with $C_{20}H_{28}O_3$. This has been confirmed by a molecular-weight determination of acetoxynorcafestenolide ($C_{21}H_{28}O_4$) made for us by Dr. I. R. Beattie and Mr. O. S. Mills using the *X*-ray crystallographic method; their detailed findings will be published separately but their value of 343·8 ± 0·6 is in good agreement with value of 344·4 required for $C_{21}H_{28}O_4$ derived from a $C_{20}H_{28}O_3$ formula for cafestol. Therefore in addition to the furan ring cafestol must contain either four carbocyclic rings or, as discussed by Djerassi and his coworkers (*loc. cit.*), it has an unreactive double bond and three carbocyclic rings as frequently found in other diterpenes. The former arrangement is preferable as we find that tetrahydrocafestol acetate is almost transparent throughout the whole measurable range of the ultraviolet absorption spectrum; the extinction of 2120 Å is of the same order as that of cholestan-3β-yl acetate, and consequently the existence of an unreactive double bond in the molecule must be excluded. The stability of epoxynorcafestanone A to vigorous treatment with hydrogen chloride or sulphuric acid, and the absence of bands at 1000—1020 cm.$^{-1}$ from the infrared spectrum of this compound or of cafestol, appear to exclude presence of a *cyclo*propane ring; it may also be noted that neither of the two compounds last named exhibits a band at 3042—3052 cm.$^{-1}$ which would correspond to a *cyclo*propane methylene group. A similar search for a *cyclo*butane ring has not been made.

The additional ultraviolet chromophore at 2900 Å present in kahweol is no doubt (as suggested by Djerassi *et al.*) due to the presence of a homoannular diene system (cf. Fieser and Fieser, *op. cit.*, p. 185) and, although very little is known about the structure of this product, it may be noted that the additional chromophore does not conjugate either with the furan ring or with the *cyclo*pentanone carbonyl group formed by oxidative elimination of the glycol side chain. Nevertheless some kind of loose interaction between the furan ring and the additional chromophore in kahweol is indicated by the progressive reduction in extinction at 2220 Å in samples of crude cafestol (or derivatives) containing increasing amounts of kahweol (or derivatives) as indicated, *inter alia*, by progressive increase in extinction at 2900 Å.

Experimental

Optical rotatory values were determined in $CHCl_3$ and ultraviolet absorption spectra were measured in EtOH.

Isolation of Cafestol.—A modification of Slotta and Neisser's method (*loc. cit.*) was used. Ground coffee beans (900 g.) which had been dried at 100° for 24 hr. were mixed with chloroform (1 l.) and shaken occasionally during 72 hr. Filtration and removal of the solvent gave a brown oil (110 g.), which was mixed with light petroleum (b. p. 40—60°; 200 c.c.) and left overnight at

0°. The precipitated caffeine was collected and the residual oil (100 g.) was introduced into well-stirred 10% aqueous sodium hydroxide (125 c.c.), and stirring continued for 3 hr. Ethanol (100 c.c.) was added, and stirring continued for a further 3 hr. Water (250 c.c.) and ethanol (90 c.c.) were added and the mixture was stirred until an almost clear solution was obtained. The solution was then continuously extracted with ether for 18 hr., and the extract, after being washed with water and dried, gave a pale brown oil which, on addition of light petroleum (b. p. 40—60°; 50 c.c.), yielded a pale yellow solid. The solid was extracted in a Soxhlet apparatus with light petroleum (b. p. 60—80°) and recovered as an almost colourless solid which was twice crystallised from light petroleum (b. p. 60—80°). The results are summarised in the Table.

Source	Yield (g.)	M. p.	$[\alpha]_D$	$\log \varepsilon_{2220}$	$\log \varepsilon_{2900}$
Dried green Santos Bourbon coffee beans	3·9	150—154°	−138° ± 3°	3·75	3·45
Coffee oil (Messrs. J. Lyons)	1·9 from 220 g. of oil	148—153	−122° ± 2°	3·76	3·10
Jamaica coffee beans	5·5	150—153	—	3·63	3·76

An attempt to utilise roasted coffee grounds from which water-soluble materials had been removed by Messrs. J. Lyons & Company Limited was not profitable because of difficulties in purification, and the poor yields of cafestol.

Purification of Cafestol.—(*a*) Crude cafestol [500 mg.; $\lambda_{max.}$ 2900 Å (log ε 3·49)] with acetic anhydride (1 c.c.) in pyridine (3·3 c.c.) gave an acetate crystallising from light petroleum (b. p. 60—80°) in needles, m. p. 159—160°, $[\alpha]_D$ −133° ± 3°, $\lambda_{max.}$ 2220 Å (log ε 3·72), 2900 Å (log ε 3·46), which gave a maleic anhydride adduct, m. p. 187—189° (decomp.) (from acetone). The acetate (400 mg.) in ethanol (20 c.c.) was shaken with hydrogen in presence of 2% palladium–charcoal (70 mg.), and after the rapid uptake (10 c.c.) ceased, pure cafestol acetate separated from light petroleum (b. p. 60—80°) in needles (360 mg.), m. p. 167—168°, $[\alpha]_D$ −89° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å (Found: C, 73·7; H, 8·7. Calc. for $C_{22}H_{30}O_4$: C, 73·7; H, 8·4%). The maleic anhydride adduct separated from acetone in cubes, m. p. 195—196° (Found: C, 68·6; H, 7·2. Calc. for $C_{26}H_{32}O_7$: C, 68·4; H, 7·0%), from which cafestol acetate, m. p. 165—167°, was recovered by refluxing with phellandrene in benzene for 20 hr. Pure cafestol acetate (500 mg.), refluxed for 3 hr. with potassium carbonate (2 g.), methanol (15 c.c.), and water (10 c.c.), gave cafestol (390 mg.), m. p. 158—159°, $[\alpha]_D$ −101° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·78), no band at 2900 Å.

(*b*) Crude cafestol [7 g.; $\lambda_{max.}$ 2900 Å (log ε 3·49)] absorbed hydrogen (161 c.c.) during 30 min., in ethanol in presence of 2% palladium–charcoal, and yielded a product, m. p. 157—159°, $[\alpha]_D$ −103° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å (Found: C, 76·1; H, 8·9%; *C*-Me, 1·1. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%). Pure cafestol gave, in benzene, a maleic anhydride adduct which crystallised from acetone in colourless needles, m. p. 191—193°.

Cafestol, prepared by method (*a*) or (*b*), did not alter in appearance after several weeks; crude cafestol, m. p. 150—154°, and containing kahweol became yellow and had m. p. 110—145° after a similar period.

Epoxynorcafestadiene.—Cafestol (1 g.), oxidised with lead tetra-acetate as described by Wettstein, Fritzsche, Hunziker, and Miescher (*loc. cit.*), yielded epoxynorcafestadienone, which crystallised from ether–light petroleum (b. p. 40—60°) in colourless needles (650 mg.), m. p. 176—178° (Found: C, 79·9; H, 8·5. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%), $\lambda_{max.}$ 2220 Å (log ε 3·80). The infrared spectrum exhibited a band at 1740 cm.$^{-1}$. A *C*-methyl determination gave 1·1 methyl groups. The semicarbazone separated from methanol in colourless needles, m. p. 244—245° (decomp.) (Found: C, 70·0; H, 7·8; N, 12·6. Calc. for $C_{20}H_{27}O_2N_3$: C, 70·4; H, 8·0; N, 12·3%). Epoxynorcafestadienone (300 mg.) in diethylene glycol (10 c.c.) containing hydrazine hydrate (90%; 300 mg.) was refluxed for 0·5 hr.; potassium hydroxide (2 g.) was added and refluxing continued for a further hour; after concentration to b. p. 190°, the solution was refluxed for a further 3 hr. and poured into water (100 c.c.); the product, isolated by continuous ether-extraction, was a pale brown oil which solidified after distillation at 160° (bath)/0·1 mm. *Epoxynorcafestadiene* separated from alcohol in colourless needles (190 mg.), m. p. 93—94° (Found: C, 84·6; H, 9·4. $C_{19}H_{26}O$ requires C, 84·4; H, 9·7%), $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å. The maleic anhydride *adduct*, prepared in cold benzene, crystallised from acetone in colourless needles, m. p. 181—182° (Found: C, 74·7; H, 7·6. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·6%).

Epoxynorcafestane.—Epoxynorcafestadiene (170 mg.) in acetic acid (20 c.c.) was hydrogenated in presence of 10% palladium–charcoal (10 mg.). After the uptake of 2 mols. of hydrogen and removal of the catalyst, the solution was diluted with water and the *product*, isolated with

ether, crystallised from aqueous methanol in colourless needles (150 mg.), m. p. 62—63° (Found : C, 82·8; H, 11·0. $C_{19}H_{36}O$ requires C, 83·2; H, 11·0%).

Ozonolysis of Epoxynorcafestadiene.—A stream of oxygen containing 2% of ozone was passed through epoxynorcafestadiene (490 mg.) in ethyl acetate (15 c.c.) cooled in acetone–carbon dioxide, until three times the calculated amount for the saturation of one double bond had been introduced. The solvent was removed under reduced pressure, the ozonide was decomposed on the steam-bath with water (10 c.c.) containing hydrogen peroxide (100-vol.; 0·4 c.c.) for 1 hr., and the products were taken up in chloroform and separated by dilute sodium hydroxide solution into neutral and acidic fractions. The neutral fraction (50 mg.) was distilled at 160° (bath)/0·1 mm., and the distillate crystallised from ether–light petroleum (b. p. 40—60°); colourless needles, m. p. 190—192° (decomp.) (Found : C, 71·1, 71·6; H, 8·0, 8·1%), were obtained which exhibited a strong band at 1737 cm.$^{-1}$ (CO). The acidic fraction (450 mg.) was distilled at 170° (bath)/0·1 mm. and yielded a glass which separated from ether–light petroleum (b. p. 40—60°) in colourless needles, m. p. 149—151° [Found : equiv., 151; C, 69·3; H, 8·7%. $C_{15}H_{24}(CO_2H)_2$ requires equiv., 147; C, 69·4; H, 8·9%], showing strong bands at 1704 and 3330 cm.$^{-1}$.

The Ketone, m. p. 126—128°.—The above dibasic acid (300 mg.) was refluxed with excess of acetic anhydride for 4 hr. and the whole set aside overnight. The mixture was poured into water and extracted with ether. The extract, washed with sodium hydrogen carbonate solution and water, gave an oil which was heated for 4 hr. at 180°/20 mm. and then distilled at 170° (bath)/0·1 mm.; a colourless oily *ketone* (130 mg.) was obtained which crystallised from methanol in irregular prisms, m. p. 126—128° [Found (on small quantity of material) : C, 81·8; H, 10·2. $C_{16}H_{24}O$ requires C, 82·7; H, 10·4%], exhibiting a band at 1740 cm.$^{-1}$ (CO).

Oxidation of Cafestol with Chromium Trioxide.—Chromium trioxide (3·6 g.) in acetic acid (80 c.c.) and water (4 c.c.) was added to cafestol (1 g.) in acetic acid (10 c.c.). After 24 hr. methanol (6 c.c.) was added and after another hour the mixture was diluted with water, and the products were isolated by continuous ether-extraction. The extract, washed with sodium hydrogen carbonate solution, yielded hydroxyoxonorcafestenolide (300 mg.) which crystallised from acetone in colourless needles, m. p. 253—254° (Found : C, 72·0; H, 7·4. Calc. for $C_{19}H_{26}O_4$: C, 72·1; H, 7·6%). The acetyl derivative, prepared with acetic anhydride in pyridine, had m. p. 235—236° (Found : C, 69·8; H, 7·3. Calc. for $C_{21}H_{28}O_5$: C, 70·4; H, 7·3%). The hydroxyoxonorcafestenolide and its acetyl derivative were apparently identical with the compounds prepared as described by Wettstein, Hunziker, and Miescher (*loc. cit.*).

Dehydration of Hydroxyoxonorcafestenolide.—The hydroxy-ketone (50 mg.) was mixed with a small amount of sodium hydrogen sulphate and distilled at 200° (bath)/0·1 mm. The distillate was sublimed at 160° (bath)/0·1 mm. and crystallised several times from alcohol; the *anhydro-derivative* was obtained as needles (30 mg.), m. p. 232—234° (Found : C, 76·0; H, 7·5. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), which gave hydroxyoxonorcafestenolide in warm methanolic sodium hydroxide. Light absorption : $\lambda_{max.}$ 2750 Å (log ε 4·16).

Hydroxycafestenolide and its Derivatives.—Ethereal monoperphthalic acid (70 c.c., containing 2·02 g. of acid) was added to epoxynorcafestadiene (1 g.); the latter rapidly dissolved and the solution was kept at 0° for 60 hr., 2·0 equivs. of per-acid being utilised. The solvent was removed under reduced pressure and the residue, extracted four times with benzene–chloroform (1·1 mixture), gave an oil (no colour with tetranitromethane). The oil was acetylated with acetic anhydride (10 c.c.) and pyridine (15 c.c.); after 24 hr. the mixture was diluted with water, and *acetoxynorcafestenolide*, isolated with ether and purified by passage through a column of alumina, crystallised from acetone–light petroleum (b. p. 60—80°) in large cubes (600 mg., m. p. 173—175° (Found : C, 73·1; H, 7·8. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%).

Hydrolysis with potassium carbonate (5 parts), methanol (70 vols.), and water (30 vols.) gave *hydroxynorcafestenolide* which crystallised from ether–light petroleum (b. p. 40–60°) in needles, m. p. 196—197° (Found : C, 75·1; H, 8·5. $C_{19}H_{26}O_3$ requires C, 75·4; H, 8·7%).

When heated for 24 hr. with *p*-tolylhydrazine hydrochloride (80 mg.) and sodium acetate (90 mg.) in aqueous methanol (90%; 5 c.c.) hydroxynorcafestenolide (50 mg.) gave a *derivative* which crystallised from ether–light petroleum (b. p. 40—60°) in yellow needles (30 mg.), m. p. 226—228° (Found : C, 80·0; H, 8·2; N, 7·3. $C_{26}H_{32}ON_2$ requires C, 80·4; H, 8·3; N, 7·2%). The *anhydro-derivative* sublimed when a mixture of hydroxynorcafestenolide and sodium hydrogen sulphate was heated at 160° (bath)/0·1 mm.; crystallisation from alcohol gave needles, m. p. 158—159° (Found : C, 80·7; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%), $\lambda_{max.}$ 2750 Å (log ε 4·17).

Chloroacetoxynorcafestenolide.—Hydroxynorcafestenolide (200 mg.) was treated in benzene

(15 c.c.) with chloroacetyl chloride (3 c.c.) and dimethylaniline (1 c.c.). After 48 hr. at 20° the mixture was shaken successively with dilute hydrochloric acid and water, and the dried benzene layer evaporated. The residue was taken up in benzene–light petroleum (b. p. 40—60°) (1 : 2) and absorbed on an alumina column, and the fraction (110 mg.) eluted with benzene–light petroleum (b. p. 40—60°) (100 c.c.; 1 : 1) crystallised from ether–light petroleum (b. p. 40—60°) in colourless plates (70 mg.), m. p. 150—151° (Found: C, 66·5; H, 6·9. $C_{21}H_{27}O_4Cl$ requires C, 66·6; H, 7·2%).

Oxidation of Epoxynorcafestadiene with Chromium Trioxide.—Epoxynorcafestadiene (1 g.) in acetic acid (10 c.c.) was oxidised at room temperature with chromium trioxide (3·5 g.) in acetic acid (70 c.c.) and water (5 c.c.). After 24 hr. the products were separated (bicarbonate) into neutral and acidic fractions. The neutral fraction, on chromatography from acetone on alumina and crystallisation from ether–light petroleum (b. p. 40—60°), gave hydroxynorcafestenolide (350 mg.), m. p. 196—197°. The acidic fraction (250 mg.) was distilled at 170° (bath)/0·1 mm., and the product separated from ether–light petroleum (b. p. 40—60°) in needles (150 mg.), m. p. 149—151°, identical with the dibasic acid obtained (*a*) by ozonolysis of epoxynorcafestadiene (p. 1988) and (*b*) by oxidising hydroxynorcafestenolide with alkaline potassium permanganate at room temperature for 12 hr.

Hydrolysis of Diacetoxyhydroxycafestenolide.—Diacetoxyhydroxycafestenolide (200 mg.), prepared from cafestol acetate as described by Wettstein, Hunziker, and Miescher (*loc. cit.*), was refluxed for 3 hr. with potassium carbonate (800 mg.) in aqueous methanol (70%; 20 c.c.). The solution was diluted with water, neutral products were removed in chloroform and ether, and the aqueous layer was acidified and extracted first with chloroform and then with ether. Evaporation of the dried combined extracts gave trihydroxycafestenolide which crystallised from acetone–light petroleum (b. p. 40—60°) in colourless needles, m. p. 234—236° (Found: C, 68·4; H, 8·3. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%).

Hydrogenation of Cafestol and its Derivatives.—Many hydrogenations were carried out on cafestol or its acetate with palladium, platinum oxide, and Raney nickel catalysts. Hydrogenation of cafestol in presence of 10% palladium–charcoal gave epoxycafestanediol, m. p. 156—157° (acetate, m. p. 152—154°, ε_{2120} 95), oxidised by lead tetra-acetate to epoxynorcafestanone A, m. p. 129—130°, ε_{2070} 197. The m. p.s of these compounds correspond with those given by Wettstein, Hunziker, and Miescher (*loc. cit.*). *Epoxynorcafestanone oxime* separated from dilute methanol in colourless needles, m. p. 192—194° (Found: N, 4·3. $C_{19}H_{29}O_3N$ requires N, 4·6%). The ketone (50 mg.) in acetic acid (15 c.c.) containing bromine (150 mg.) was kept for 24 hr. in the dark at room temperature; the *tribromo-derivative* separated from dilute acetic acid in nodules, m. p. 110—114° (Found: C, 43·5; H, 4·4; Br, 45·3. $C_{19}H_{25}O_3Br_3$ requires C, 43·5; H, 4·8; Br, 45·6%).

Reduction of cafestol acetate (1·06 g.) in acetic acid (40 c.c.) in presence of platinic oxide (0·28 g.) at room temperature and pressure resulted in the uptake of 2·5 mols. of hydrogen. Chromatography of the product on alumina (25 g.) gave a heterogeneous fraction (90%) on elution with benzene and ether, but elution with acetone gave a fraction (10%), m. p. 179—180°. The latter fraction (hydrogenolysis product) gave a *diacetyl derivative* which crystallised from light petroleum (b. p. 40—60°) in colourless nodules, m. p. 81° (Found: C, 70·7; H, 9·1. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·3%). Hydrolysis of the earlier fractions (monoacetates) and oxidation with chromium trioxide in acetic acid yielded a mixture apparently of epoxynorcafestanone A, m. p. 131—132°, and epoxynorcafestanone B, m. p. 165—166°; these ketones, with the same m. p.s, were obtained by Wettstein, Fritzsche, Hunziker, and Miescher (*loc. cit.*) from cafestol acetate by hydrogenation, hydrolysis, and oxidation with periodic acid.

Methyl Tetrahydrovinhaticoate.—Our thanks are offered to Professor F. E. King, F.R.S., for a generous gift of methyl vinhaticoate which was hydrogenated as described by King, King, and Neill (*J.*, 1953, 1055); the *product* separated from methanol in colourless needles, m. p. 90—91° (Found: C, 74·9; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·3%).

Our thanks are offered to British Schering Limited and to Drs. E. B. Hughes and L. H. Lampitt of Messrs. J. Lyons & Company Limited for gifts of cafestol, coffee-bean oil, and coffee grounds, to Dr. G. D. Meakins of Manchester University and Imperial Chemical Industries Limited, Billingham Division, for some of the infrared measurements, to Imperial Chemical Industries Limited for a grant towards the expenses of this research, and to the Department of Scientific and Industrial Research for a maintenance allowance to one of us (A. H. J.).

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An Empirical Bond-additivity Method for the Calculation of Diamagnetic Susceptibilities of Simple Organic Molecules.

By C. M. FRENCH and D. HARRISON.

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The Pascal system of calculating susceptibilities of diamagnetic organic molecules is composed of (*a*) atomic and bond constants and (*b*) structural correction terms. The constants of (*a*) are equivalent to a set involving bond terms only.

A modified bond-additivity system is described, in which the structural correction terms take the form of "bond interactions," the results obtained being compared with some recent experimental values. Where the Pascal system gives poor results, the new system often appears more reliable. For the relatively simple compounds studied, few serious differences have been found between experimental and calculated values. The possible extension of the system to more complex structures is briefly indicated, and attention drawn to the frequently rather large variations between different authors' experimental values.

CALCULATION of the diamagnetic susceptibilities of the simplest organic molecules, by purely theoretical methods, has as yet failed to yield values in even approximate agreement with experiment. For instance, all values for methane are much too high. In the absence of a satisfactory theoretical treatment a system of a type devised by Pascal, and recently reviewed and modified by Pacault (*Rev. sci.*, 1948, **86**, 38), can be of great value for the correlation of experimental data and for the investigation of structural problems. Recent results (Trew, *Trans. Faraday Soc.*, 1953, **49**, 604; Angus, *Bull. Soc. chim. France*, 1949, **16**, *D*, 483; Broersma, *J. Chem. Phys.*, 1949, **17**, 873) demonstrate that the method is not entirely satisfactory for all simple organic compounds. The constants suggested by Broersma (*loc. cit.*) give better results for some compounds but his method contains certain undesirable features. Contrary to the views expressed by Pascal, Pacault, and Hoarau (*Compt. rend.*, 1951, **233**, 1078) differences between calculated and experimental values cannot always be removed by modification of numerical constants, particularly for branched-chain hydrocarbons and alkyl halides.

A new empirical system of calculation of magnetic susceptibility is now presented which appears to avoid some of the difficulties encountered with the Pascal system. Only a limited number of structural types has so far been dealt with, but it is hoped to extend these later. The present system has been developed along lines suggested partly by analogy with recent theoretical treatments of other additive properties in such compounds. A considerable simplification is made possible by the use of the following characteristic property of additivity systems.

Ideal Additivity Systems.—Consider the structures which can be built up from r different elements, using only single or multiple covalent bonds, and where each particular element displays only a single numerical valency throughout. Suppose that for every one of these structures, the numerical value of some property P can be represented by the equation:

$$P = \sum_{J} n_J \cdot p_J + \sum_{JK} n_{JK} \cdot p_{JK} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n_J is the number of J atoms in the structure, p_J a constant characteristic of the atom J, n_{JK} the number of J–K bonds (single and multiple bonds being considered separately), and p_{JK} a constant for the bond J–K.

Under these conditions, the property P can be described as satisfying an "ideal additivity system," consisting of the constants p_J, p_{JK}, etc. Although an unlimited number of equations such as (1) can be written for different structures, the maximum number of these which can be independent is s, the total number of different bond types. There are however $(r + s)$ unknowns, so that the constants of the additivity system are not uniquely defined by the observed P values, and in fact there is an infinite number of different sets of

constants which will satisfy the equations. A particular additivity system is defined by giving arbitrary values to *any r* of the constants: the remaining *s* constants can then be determined by solution of the equations for *s* experimentally measured structures (the " reference standards "). Since for every structure there exists a linear relation between the numbers of atoms and of bonds, it can be proved that all the additivity systems derived from the same set of reference standards will give the same calculated value for *P* of any compound outside the reference set.

The same result will hold if an " average " member of an homologous series is taken as reference standard, instead of a single substance. A formal proof of this property of ideal additivity systems is given in the Appendix, for the case of compounds containing the elements carbon, hydrogen, and oxygen only.

The Pascal System.—The set of constants given by Pascal can be divided into two distinct types of term, represented by A and B such that:

$$\chi = \sum A + \sum B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where χ is the *molar* diamagnetic susceptibility (usually denoted by χ_m). $\sum A$ consists of the constants of an ideal additivity system, as defined above, whilst $\sum B$ contains only structural correction terms. This division, although not always clear in the original form of the system, can be achieved by simple manipulation. Now since $\sum A$ and $\sum B$ are completely independent, the result of the previous section can be applied to $\sum A$. In forming $\sum A$, Pascal assigned values to bonds and atoms in very arbitrary fashion, *e.g.*, all single bonds were given zero bond term, and some atoms, such as carbonyl-oxygen, had bond and atomic terms combined. An entirely equivalent system can be constructed, in which all atomic terms are zero, and a bond term is assigned to every bond in the molecule, $\sum B$ being retained in its original form. This system will give results identical with those of the Pascal system in all cases, provided suitable values are assigned to the bond constants. Pascal, Pacault, and Hoarau (*loc. cit.*) gave a set of bond constants equivalent to the atomic and bond constants of their revised Pascal system. They attributed the equivalence of the two systems to the fact that in compounds of the lighter elements, the main contribution to the diamagnetism arises from the electrons of the bonds. This assertion, even if justified, is not needed to explain the equivalence of the two systems, which arises from the properties of ideal additivity systems. In the new system proposed here, all atomic constants will be taken as zero, and the structural correction terms for simple molecules will be expressed in a somewhat different, and more systematic, form.

The Modified Bond-additivity System.—The observation that the diamagnetic susceptibility of an unconjugated molecule could be expressed as the sum of terms characteristic of the various bonds might be most simply interpreted as indicating that the bonding electrons are accommodated in completely localised molecular orbitals, each pair of bonding electrons contributing a characteristic amount to the observed susceptibility. Contributions from inner-shell electrons would, by arguments previously adduced, be capable of inclusion in the bond terms. This is an over-simplification, and Dewar and Pettit (*J.*, 1954, 1625) found that, in order to obtain a satisfactory interpretation of the heats of formation of some series of aliphatic compounds, it was necessary to use a perturbation method in which the localised bond structure was taken as the unperturbed system, and the bond interactions as small perturbations. In a similar way it would seem reasonable to take the deviations of the diamagnetic suceptibilities of simple aliphatic molecules from bond additivity as second-order perturbation terms arising from bond interactions. Although the analogy must not be pressed too far, agreement between calculated and experimental susceptibilities obtained so far indicates that it is not unreasonable.

In order to keep the number of bond interaction terms within reasonable limits, two assumptions are made: (*a*) that in unconjugated systems only " nearest-neighbour " interactions are important, and (*b*) that interactions involving bonds in which one atom is hydrogen can be neglected. The second assumption is the more serious, but is supported by Altmann's work (*Proc. Roy. Soc.*, **1951**, *A*, **210**, 327; see also Dewar and Pettit, *loc. cit.*).

The values of the constants of the system presented here have been deduced from experimental results published within the last 12 years which, though not comprehensive, are thought to be fairly representative. The sources used are listed at the foot of Table 3. Application of the method to various classes of compound reveals the following particular features.

(a) *Saturated aliphatic hydrocarbons.* Recent work by Trew (*loc. cit.*) has shown the existence of an " end-effect " in the lower members of this series. Since definite evidence has yet to be published of a similar effect in other homologous series, no attempt will be made to include, in the present treatment, terms allowing for an end-effect. Instead, compounds containing less than seven carbon atoms will not be considered.

By analogy with Dewar and Pettit's result (*loc. cit.*), it might be expected that for a straight-chain hydrocarbon C_nH_{2n+2}:

$$\chi_n = (2n + 2)\chi_{C\text{-}H} + (n - 1)\chi_{C\text{-}C} + (n - 2)\lambda_{C\text{-}C\text{-}C} \quad . \quad . \quad . \quad . \quad (3)$$

where $\chi_{C\text{-}H}$, etc., are bond terms, and $\lambda_{C\text{-}C\text{-}C}$ is an interaction term. (All susceptibility values in this and following sections are recorded in 10^{-6} c.g.s. units and the negative signs are omitted.) Since the bond terms have no theoretical significance, an arbitrary value of $\chi_{C\text{-}C}$ which includes $\lambda_{C\text{-}C\text{-}C}$ may be employed, and this procedure will be adopted in the following discussion.

Equation (3) then becomes:

$$\chi_n = (2n + 2)\chi_{C\text{-}H} + (n - 1)\chi_{C\text{-}C} - \lambda_{C\text{-}C\text{-}C} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The one term $-\lambda_{C\text{-}C\text{-}C}$ must be retained since there is one less interaction term than C–C bond terms.

Similarly for the hydrocarbon $C_{n+1}H_{2n+4}$

$$\chi_{n+1} = (2n + 4)\chi_{C\text{-}H} + n\chi_{C\text{-}C} - \lambda_{C\text{-}C\text{-}C} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

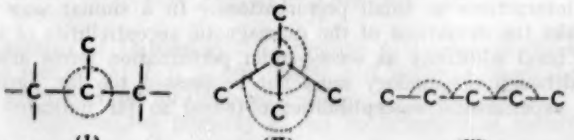
In a branched-chain saturated hydrocarbon with one tertiary carbon atom, three C–C–C bond interactions may be considered in the unit (I) as represented by broken lines. In a linear hydrocarbon with the same number of carbon atoms, there would be only two such interactions C–C–C–C. If the values of the $\lambda_{C\text{-}C\text{-}C}$ were numerically the same for both cases, as present experimental data indicate, then, for the branched-chain hydrocarbon:

$$\chi_n' = (2n + 2)\chi_{C\text{-}H} + (n - 1)\chi_{C\text{-}C} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This assumption may, however, be an over-simplification (which might be shown by subsequent more precise experimental measurements) and in that case an extra term λ_3 must be introduced to denote the value for the extra C–C–C interaction due to the tertiary carbon atom; so if there are m_3 such tertiary atoms, then:

$$\chi_n' = (2n + 2)\chi_{C\text{-}H} + (n - 1)\chi_{C\text{-}C} - \lambda_{C\text{-}C\text{-}C} + m_3\lambda_3 \quad . \quad . \quad . \quad (7)$$

Application of these equations to Trew's results (*loc. cit.*) enables the various constants to be evaluated. The numerical values giving best agreement over the whole series of compounds measured are given in Table 1.



(I) (II) (III)

Equation (7) implies that each additional tertiary carbon atom produces the same increase (1·4 units) in diamagnetism. There is some indication that when tertiary carbon atoms are close together their total effect is somewhat reduced, but Trew's results for isomeric decanes are consistent with equation (6) within the limits of experimental error.

Similarly, if there is a quaternary carbon atom, it might be supposed that there are six C–C–C interactions [cf. (II)] instead of three for the corresponding linear hydrocarbon [cf. (III)]. Hence, if it could be assumed that all these interactions were equal, then for a C_n hydrocarbon containing m_4 quaternary carbon atoms:

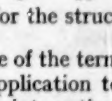
$$\chi_n'' = (2n + 2)\chi_{\text{C-H}} + (n - 1)\chi_{\text{C-C}} - (1 - 3m_4)\lambda_{\text{C-C-C}} \quad . \quad . \quad . \quad (8)$$

This equation is, however, not satisfied by the available data. However, an equation in reasonable agreement with experiment can be obtained by replacing the term $3m_4\lambda_{\text{C-C-C}}$ by $m_4\lambda_4$, where λ_4 is a constant for the three extra terms and is considerably less than $3m_4\lambda_{\text{C-C-C}}$. Thus for a hydrocarbon $C_nH_{2n+2}(n > 7)$ with m_3 tertiary and m_4 quaternary carbon atoms:

$$\chi = (2n + 2)\chi_{\text{C-H}} + (n - 1)\chi_{\text{C-C}} - \lambda_{\text{C-C-C}} + m_3\lambda_3 + m_4\lambda_4 \quad . \quad . \quad . \quad (9)$$

There is a close analogy between this result and that obtained by the use of group susceptibilities as suggested by Trew (*loc. cit.*).

(b) *Alkylbenzenes.* Broersma's and Trew's results (*locc. cit.*) on monoalkylbenzenes indicate that there is an abnormally low CH_2 increment in passing from benzene to toluene, but that subsequent lengthening of the carbon chain produces an increment of almost constant magnitude, with the normal value of 11·7 units. This is in harmony with spectroscopic and chemical evidence that the difference in conjugative effect of different alkyl groups is relatively small, as pointed out for instance by Dewar and Pettit (*loc. cit.*). In consequence, the susceptibilities of the monoalkylbenzenes can be reasonably accounted for by introduction of a single interaction term $\lambda_{\text{Ph-C}}$, representing the interaction of the benzene ring with the first C–C bond attached to it. Two additional points concerning the calculation of the susceptibilities of alkylbenzenes must be noted, (*a*) that $-\lambda_{\text{C-C-C}}$ must be included in all cases (except for benzene itself), and (*b*) that the nuclear carbon atom to which the side chain is attached is not regarded for the present purpose as a tertiary carbon atom. Further it is convenient to define a quantity $\chi_{\text{C-C(ar)}} = 5{\cdot}14$, such that the molar susceptibility of benzene $= 6\chi_{\text{C-C(ar)}} + 6\chi_{\text{C-H}}$. The small amount of recent work on dialkylbenzenes is insufficient to extend the system to such structures at present. It does appear that terms depending on the relative orientation of the substituents may be necessary.

(c) *Oxygen-containing compounds.* The available data on these compounds are consistent with the assumption that the three interaction terms $\lambda_{\text{C-C-C}}$, $\lambda_{\text{C-C-O}}$, and $\lambda_{\text{C-O-C}}$ are roughly equal and have a value of 1·4 units. The calculation of the susceptibilities of certain of these compounds can be simplified by defining a " tertiary " carbon atom as one in a structure  , in which X is either C or O. A " quaternary " carbon is similarly defined for the structure . These definitions include as special cases the conventional use of the terms in connection with the hydrocarbons. In case of doubt with regard to the application to complex structures, the alternative, but longer, method of writing down the interaction terms in full can be used, but this requires more care in dealing with compounds such as tertiary alcohols. As an example of the simpler method of calculation the susceptibility of propan-2-ol can be expressed as:

$$\chi = 7\chi_{\text{C-H}} + 2\chi_{\text{C-C}} + \chi_{\text{C-O}} + \chi_{\text{O-H}} - \lambda_{\text{C-C-C}} + \lambda_3 + \lambda_{\text{C-C-O}}$$

The particular choice of $\chi_{\text{C-O}}$ made here, necessitates the inclusion of $\lambda_{\text{C-C-O}}$ in the calculated susceptibility of any alkoxy-group (primary, secondary, or tertiary) in addition to λ_3 or λ_4 where necessary. This convention avoids difficulties which would otherwise arise in compounds containing a " quaternary " carbon atom. The values of $\chi_{\text{C-O}}$ and $\chi_{\text{O-H}}$ given in Table 1 were derived principally from Angus and Hill's results (*Trans. Faraday Soc.*, 1943, **39**, 185). Very recently Sacconi and Cini (*Atti Accad. naz. Lincei*, 1954, **14**, 237) published results for a number of alcohols, which they claim to have great accuracy. Their values are on the whole 1—2% higher than those of Angus and Hill, but the increments between different members of the series are roughly the same. If these higher values are substantiated, slightly higher values of $\chi_{\text{C-O}}$, $\chi_{\text{O-H}}$, or perhaps $\lambda_{\text{C-C-O}}$ will be needed. This

adjustment, which would necessarily involve many other terms too, would seem to be as yet somewhat premature.

No extensive measurements on simple aldehydes and ketones have yet been undertaken. According to Angus (*Nature*, **1946**, **158**, 705), the aliphatic aldehydes have slightly greater susceptibilities than the isomeric ketones, the difference being of the order of 0·6 unit. From this evidence a tentative value of $\lambda_{C\text{-}C=O} = -0{\cdot}6$ will be assumed. This value does not apply in carboxylic acid derivatives, where the corresponding term is practically zero. This difference is hardly surprising in view of the very different nature of a carbonyl group in the two classes of compound.

In dealing with aromatic acids, esters, ketones, etc., only two new terms are required. One of these is $\lambda_{Ph\text{-}O}$, analogous to $\lambda_{Ph\text{-}C}$ already discussed, and is a term used when an oxygen atom is directly attached to the benzene ring. The second arises in structures such as benzoic acid, where, for the first time in this work, we have to deal with a conjugated system (with the exception, of course, of the aromatic nucleus itself). The effect of simple conjugation on diamagnetic susceptibilities can be included in the system, by introduction of interaction terms between pairs of conjugated double bonds, or a double bond and an aromatic nucleus, one C–C bond apart. The term required here will be denoted $\lambda_{Ph\text{-}C=O}$. As in the case of $\lambda_{C\text{-}C=O}$, it is not surprising to find that a somewhat different value of $\lambda_{Ph\text{-}C=O}$ is required in carboxylic acid derivatives from that in aldehydes and ketones.

In the above discussion, no account has been taken of the possibility that the interaction term between two bonds may depend on the angle between them. Where the compounds considered contain oxygen atoms and double bonds, there will almost certainly be considerable variations in inter-bond angles, but the results obtained so far indicate that to a first approximation this effect can be neglected.

(d) *Alkyl halides.* Here again, the experimental data are satisfied by use of an interaction term $\lambda_{C\text{-}C\text{-}Cl} = \lambda_{C\text{-}C\text{-}Br} = 1{\cdot}4$. Thus the definition of "tertiary" and "quaternary" carbon atoms given previously can be extended to include X = Cl and Br. Calculation of the susceptibility of a particular alkyl halide then follows exactly the method used for an alcohol, *e.g.*, for *iso*propyl chloride, $(CH_3)_2CHCl$:

$$\chi = 7\chi_{C\text{-}H} + 2\chi_{C\text{-}C} + \chi_{C\text{-}Cl} - \lambda_{C\text{-}C\text{-}C} + \lambda_3 + \lambda_{C\text{-}C\text{-}Cl}$$

Values for terms such as $\lambda_{Ph\text{-}Cl}$ have not yet been deduced, since they can be obtained only from the experimental value for a single compound (*e.g.*, chlorobenzene), no independent check being possible. It is also possible that in compounds of the type of benzyl chloride a small interaction term may be needed for bonds which are not "nearest neighbours," but the small amount of evidence on this point is indecisive.

Table 1 gives the numerical values of the constants so far derived.

TABLE 1. *Provisional values of bond and interaction terms.*

(a) *Bond terms* ($\chi_{X\text{-}Y}$).

X–Y	C–C	C–H	C–C(ar)	C–O	C=O	O–H	C–Cl	C–Br
$\chi_{X\text{-}Y}$	3·70	4·00	5·14	3·15	5·10	5·85	20·10	30·8

(b) *Interaction terms.*

$\lambda_{C\text{-}C\text{-}C} = \lambda_{C\text{-}C\text{-}O} = \lambda_{C\text{-}O\text{-}C} = \lambda_{C\text{-}C\text{-}Cl} = \lambda_{C\text{-}C\text{-}Br} = \lambda_3 = 1{\cdot}4$

$\lambda_4 = 2{\cdot}1$

$\lambda_{C\text{-}C=O} = 1{\cdot}8 \quad \lambda_{Ph\text{-}C} = 0{\cdot}3 \quad \lambda_{Ph\text{-}O} = 0{\cdot}9$

$\lambda_{C\text{-}C=O} = -0{\cdot}6$ (aldehydes and ketones); 0 (carboxylic acid derivatives)

$\lambda_{Ph\text{-}C=O} = -0{\cdot}3$ (aldehydes and ketones); 0 (carboxylic acid derivatives)

Comparison of Results given by the Pascal System, with those of the Modified Bond-additivity System.—From the sources listed at the foot of Table 3, experimental values are available for 95 compounds, to which the constants of Table 1 should be applicable (the lower hydrocarbons, and some compounds in which tautomeric possibilities arise, are not included). For each of these compounds, the experimental susceptibility has been compared with the values calculated by (*a*) Pascal's method, numerical values given by Pacault (*loc. cit.*) being employed, and (*b*) the modified bond-additivity method. Unfortunately, it is not uncommon to find considerable differences in the values for a particular

substance reported by different workers. For instance, the values recorded for methyl acetate include 42·37 (Angus and Hill, *loc. cit.*), 42·6 (Broersma, *loc. cit.*), and 43·51 (French, *Trans. Faraday Soc.*, 1947, **43**, 356). In such cases, in order to make a fair comparison, the mean of those values which are in reasonable agreement has been used, a widely divergent value being omitted. Where there is no reasonable agreement between reported values, *e.g.*, for ethyl propionate, 65·75 (Angus and Hill, *loc. cit.*), 66·51 (Broersma, *loc. cit.*), the substance has been omitted from consideration since it is evident that a redetermination is necessary.

This procedure left a total of 85 compounds, for which the bond-additivity method gave a value within 1% of the experimental mean in all but 11 cases; of these exceptions, 9 were compounds for which only a single experimental value is available. On account of the divergences in experimental values, all figures were taken only to the nearest 0·1 unit. Table 2 gives some examples of compounds in which good agreement was obtained. It can be clearly seen that in some cases both methods give results in reasonable agreement with experiment, but in others where the Pascal system is apparently unsatisfactory, the new method gives a more reliable value. Table 3 illustrates a few of the cases in which the results of the bond-additivity method are not satisfactory.

TABLE 2.

Substance	Mean exp. χ	Calculated χ Bond system	Pascal	Substance	Mean exp. χ	Calculated χ Bond system	Pascal
n-Octane	96·5 [1,2]	96·5	100·7	*iso*Pentyl formate	78·4 [6]	78·8	79·6
4-Methyloctane	109·6 [1]	109·6	112·6	Ethyl *iso*butyrate	78·3 [4]	78·8	80·4
4 : 5-Dimethylnonane	134·5 [1]	134·7	136·3	*n*-Propyl benzoate	105·0 [6]	104·8$_5$	106·1
2 : 2 : 3-Trimethylpentane	99·9 [3]	100·0	100·7	Phenyl acetate	82·0 [6]	82·0$_5$	82·0$_5$
Toluene	65·8 [1,2,3]	65·4$_5$	66·8	Benzyl formate	81·4 [6]	81·1$_5$	82·0$_5$
n-Butylbenzene	100·8 [1]	100·5$_5$	102·4	Ethyl phenylacetate	104·7 [6]	104·7$_5$	105·0
4 : 6 : 6-Trimethyl-1-phenylheptane	173·9 [1]	174·2$_5$	173·6	Acetone	33·9$_5$ [2,4,7]	33·9	33·9
n-Butyl alcohol	56·0 [2,4]	56·0	57·9	Propiophenone	84·5 [6]	84·4	84·5
sec.-Butyl alcohol	57·3 [4]	57·4	57·9	*iso*Butyl chloride	68·6 [5]	68·6	70·3
n-Butyric acid	55·1 [2,4,5]	55·0	55·4	Diethyl succinate	104·8 [5,9]	105·1	104·9
				Ethylene glycol	38·8 [3]	39·1	38·8
				Diethyl ether	55·1 [3]	55·1	57·9

TABLE 3.

Substance	Mean exp. χ	Calculated χ Bond system	Pascal	Substance	Mean exp. χ	Calculated χ Bond system	Pascal
2 : 2 : 4-Trimethylpentane	98·3 [3]	100·0	100·7	Ethyl formate	43·2 [2,4]	42·3	43·5
				*iso*Propyl oxalate	106·0 [9]	107·9	104·9

Refs.: [1] Trew, *loc. cit.* [2] Broersma, *loc. cit.* [3] Baddar and Sugden, *J.*, 1951, 308. [4] Angus and Hill, *loc. cit.* [5] French, *loc. cit.* [6] Angus, *loc. cit.* [7] French and Trew, *Trans. Faraday Soc.*, 1945, **41**, 439. [8] Cherrier, *Compt. rend.*, 1948, **226**, 1016. [9] Angus and Stott, *Trans. Faraday Soc.*, 1953, **49**, 680.

It is concluded that the system of additive bond susceptibilities and bond interaction terms presented here is more reliable for the prediction of the diamagnetic susceptibility of these simple structures than the Pascal system, even as modified by Pacault. Further, because of the relation between the ideal additivity portion of the Pascal system to that of the system presented here, it is possible to transfer any part of the Pascal–Pacault system, which is in itself satisfactory, *e.g.*, the treatment of polycyclic and heterocyclic systems, into the new system, without interfering with the existing bond terms.

APPENDIX

Consider the structures which can be built up from the elements carbon, hydrogen, and oxygen, using the following seven bond types:

(1) C–C; (2) C=C; (3) C≡C; (4) C–H; (5) C–O; (6) C=O; (7) O–H

If for these structures the property P satisfies an ideal additivity system, then for the structure α, equation (1) takes the form:

$$P = n^{\alpha}_{C} \cdot P_{C} + n^{\alpha}_{H} \cdot p_{H} + n^{\alpha}_{O} \cdot P_{O} + n^{\alpha}_{1} \cdot p_{1} + \ldots . n^{\alpha}_{7} \cdot p_{7} \quad . \quad . \quad . \quad (10)$$

where n^{α}_{C}, n^{α}_{H}, and n^{α}_{O} are the number of carbon, hydrogen, and oxygen atoms and n^{α}_{1}, n^{α}_{2} . . . . the number of bonds of types 1, 2 . . . . By examination of a few simple formulæ it can easily be deduced that:

$$4n^{\alpha}_{O} = 2n^{\alpha}_{1} + 4n^{\alpha}_{2} + 6n^{\alpha}_{3} + n^{\alpha}_{4} + n^{\alpha}_{5} + n^{\alpha}_{6} \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

$$n^{\alpha}_{H} = n^{\alpha}_{4} + n^{\alpha}_{7} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$2n^{\alpha}_{O} = n^{\alpha}_{5} + 2n^{\alpha}_{6} + n^{\alpha}_{7} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

By use of these three equations, n^{α}_{C}, n^{α}_{H}, and n^{α}_{O} can be eliminated from equation (10). Rearranging the resulting equation, we have

$$\begin{aligned} P = {} & n^{\alpha}_{1}(p_1 + p_C/2) + n^{\alpha}_{2}(p_2 + p_C) + n^{\alpha}_{3}(p_3 + 3p_C/2) + n^{\alpha}_{4}(p_4 + p_C/4 + p_H) \\ & + n^{\alpha}_{5}(p_5 + p_C/4 + p_O/2) + n^{\alpha}_{6}(p_6 + p_C/4 + p_O) + n^{\alpha}_{7}(p_7 + p_H + p_O/2) \\ = {} & n^{\alpha}_{1} \,.\, R_1 + n^{\alpha}_{2} \,.\, R_2 + \ldots . n^{\alpha}_{7} \,.\, R_7 \quad . \quad . \quad . \quad . \quad . \quad (14) \end{aligned}$$

where $R_1 = p_1 + p_C/2$; $R_2 = p_2 + p_C$; etc.

Since an equation similar to (10) can be written for every structure considered, it follows that the value of P in every case can be expressed as a linear function of seven R terms. Thus only a maximum of 7 independent equations can be written, these being assigned to the reference standards. The numerical values of P specify only the R's, not the individual bond and atomic constants, which can be assigned in any way consistent with the conditions $R_1 = p_1 + p_C/2$, etc. The infinite number of systems defined in this way will give the same calculated value for any compound outside the reference standards, since the susceptibility in all cases will depend only on R_1, R_2, etc., which are the same in all systems. It is important to note that in defining a particular additivity system, in the cases where R is the sum of two terms only, *e.g.*, R_1, R_2, and R_3 in the above example, both terms in a particular R must not be assigned arbitrary values, otherwise the equation may prove to be inconsistent. A co-ordinate linkage, *e.g.*, C→O, could be included in the list of bonds considered, since a relation would still exist between the various n's, if not quite such a simple one as when only covalent bonds were considered.

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Oxidation of Organic Sulphides. Part IV. Autoxidation of cyclo*Hex-2-enyl *Methyl Sulphide.*

By L. BATEMAN and F. W. SHIPLEY.

[Reprint Order No. 5917.]

*cyclo*Hex-2-enyl methyl sulphide readily absorbs up to *ca.* 0·3 mole of oxygen per mole at 55° to yield a complex mixture. *cyclo*Hexenyl methyl sulphoxide, 6-methylthio*cyclo*hex-2-enone (VIII), *cyclo*hexenone, *cyclo*hexenol, water, and dimethyl disulphide have been identified and estimated approximately quantitatively. A reaction mechanism consistent with these and other experimental data is presented and discussed.

Several new keto-sulphides which were required as reference compounds have been prepared and characterized; the sulphide (VIII) and its 3-methylthio-isomer (III) show marked antioxidant activity.

THE autoxidizability of allylic sulphides is characterized by a rapid initial uptake of oxygen which later falls to a negligible rate when only a fraction of a mol. of oxygen has been absorbed (Part III *). One or more of the reaction products must be responsible for this autoinhibition, and this paper describes the first of a series of investigations into what these are and how they act. *cyclo*Hex-2-enyl methyl sulphide (I) was chosen as the first sulphide for detailed study because it is readily obtained pure (in particular, contamination with

* Part III, *J.*, 1955, 1596.

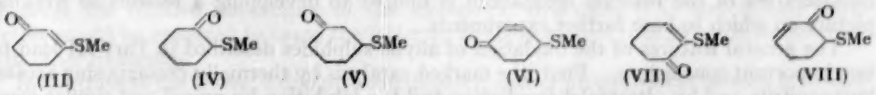
allylic isomerides is impossible) and because it absorbs more oxygen before reaction ceases than most other sulphides so far examined.

When the sulphide (I) was shaken in oxygen at 55°, it absorbed about 0·3 mole of oxygen per mole before further reaction became negligible. The solution was cloudy and contained water droplets. About a quarter of the absorbed oxygen was combined in sulphoxide groups, as estimated by reduction with titanous chloride (Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 536).

The reaction mixture was separable by distillation into fractions (i) b. p. 60—70°/14 mm., (ii) b. p. 80—90°/0·1 mm., and (iii) a dark residue involatile at 0·1 mm. Fraction (i) consisted of unchanged sulphide admixed with water, dimethyl disulphide, *cyclo*hex-2-enone, and *cyclo*hex-2-enol. The last two compounds were identified spectroscopically and by the derivatives given with 2 : 4-dinitrophenylhydrazine and α-naphthyl *iso*cyanate, respectively. Fraction (ii) analysed approximately for $C_7H_{11}OS$ and had a sulphoxide content about half that of the nearly isomeric *cyclo*hex-2-enyl methyl sulphoxide (II). Fraction (iii), which also had a substantial sulphoxide content, proved to be mainly the decomposition products formed during distillation (see below) and was not examined in detail.

While the infrared spectrum of fraction (ii) and its reaction with 2 : 4-dinitrophenylhydrazine showed a considerable amount of carbonyl-containing material to be present, attempts at separation by further fractionation proved fruitless. Two other procedures, however, were successful: (*a*) treatment with titanous chloride reduced the sulphoxide to the original sulphide, which could be distilled from the reduced product to leave a heterogeneous keto-sulphide (KS), b. p. 67—70°/0·1 mm.; (*b*) chromatography using silica gel permitted both the sulphoxide (II) and the mixture (KS) to be recovered separately and characterized. Chromatography of the original reaction mixture (after drying) afforded a more thorough, but for sizeable quantities more laborious, overall separation; its application to quantitative estimation of the constituents is described later. Under these mild conditions, the amount of involatile product isolated [fraction (iii) above] was very small.

Composition of the Keto-sulphide (KS).—Elemental analyses and the molecular weight corresponded to the formula $C_7H_{10.7}OS$. Desulphurization with Raney nickel gave *cyclo*hexanol in good yield, thus proving the presence of a cyclic C_6 unit with the oxygen atom attached. The infrared and ultraviolet spectra were complex, but indicated the presence of unconjugated and variously conjugated keto-groups, the simple αβ-unsaturated form being predominant. Weak absorption at 1570 cm.$^{-1}$ suggested the presence of about 5% of a triply conjugated chromophore as occurs in (III), and this was consistent with absorption at 1655 cm.$^{-1}$ attributed to a highly conjugated ketone group. Ultraviolet absorption at 2900—3000 Å was also consistent, but this proved to be non-critical evidence since differently substituted *cyclo*hexenones were found to absorb similarly (see below).



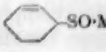
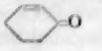
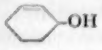
On treatment with 2 : 4-dinitrophenylhydrazine in aqueous hydrochloric acid, a solid derivative, m. p. 168—180°, was obtained in high yield. Non-selective ultraviolet absorption of this product reflected the complexity of the parent ketone. Paper chromatography showed a weak and a strong spot which had R_F values of 0·38 and 0·19, respectively, under the conditions described on p. 2002. The first of these is attributed to the 2 : 4-dinitrophenylhydrazone of a saturated keto-sulphide, since the corresponding derivatives of 2- and 3-methylthio*cyclo*hexanone (IV and V) behave similarly; the second is derived from an unsaturated keto-sulphide, but of uncertain type since the dinitrophenylhydrazones of the differently conjugated 3- and 4-methylthio*cyclo*hex-2-enone (III and VI) have the same R_F value. Fractional crystallization gave a small yield of a derivative of an unidentified saturated keto-sulphide, possibly of 4-methylthio*cyclo*hexanone since it

is not (IV) or (V), which were independently synthesized and characterized, while the major constituent consisted of dark red needles, m. p. 235°, having an absorption peak in the near ultraviolet at 3750 Å ($E^{1\%}_{1\,cm.}$ 821). These spectral features are intermediate to those shown by the corresponding derivatives of the triply conjugated keto-sulphide (III) ($\lambda_{max.}$ 2650, 3020, 4000 Å; $E^{1\%}_{1\,cm.}$ 410, 398, 939) and the unconjugated compound (V) ($\lambda_{max.}$ 3630 Å; $E^{1\%}_{1\,cm.}$ 743), and hence were associated with a parent αβ-unsaturated ketone structure. The 2 : 4-dinitrophenylhydrazone of *cyclo*hexenone absorbs similarly ($\lambda_{max.}$ 3750 Å; $E^{1\%}_{1\,cm.}$ 994), and so does the derivative later prepared from (VI) ($\lambda_{max.}$ 2500, 3740 Å; $E^{1\%}_{1\,cm.}$ 552, 880), which is otherwise distinguishable from the unknown. Examination of the corresponding semicarbazones led to the same conclusion.

If the double bond is not involved in more than one displacement from its original position in (I), *i.e.*, oxygen attachment is confined to position 1, 2, 3, or 4 (see Part III, *loc. cit.*), the main constituent of (KS) must be either (VII) or (VIII). Reduction with lithium aluminium hydride gave an alcohol which absorbed far less intensely at 2300 Å than a substituted vinyl sulphide such as would be derived from (VII). Positive identification was finally achieved by the synthesis of (VIII) and direct comparison of the synthetic ketone and its derivatives with the unknown.

Quantitative Estimation of the Products.—The sulphoxide content was determined directly on the oxidized mixture as mentioned above. Dimethyl disulphide was estimated from a separate experiment. The more volatile fraction of the total oxidation mixture was distilled off and reduced with lithium aluminium hydride, and the resulting thiol estimated by the copper acetate method. Water was determined in a number of separate experiments in which it was distilled from the reaction mixture as its benzene azeotrope and then determined by the Karl Fischer procedure. For the remaining products, the reaction mixture was dried, diluted with light petroleum, and passed through a column of silica gel. After removal of the original sulphide and dimethyl disulphide with successive petroleum washings, the column was eluted with petroleum containing 10—50% of ether to remove *cyclo*hexenone, *cyclo*hexenol, and the keto-sulphides. These components could not be separately determined directly in the mixture, but approximate analysis was possible by separating the first two compounds from the third by distillation and then applying spectroscopic and polarographic methods.

Oxygen Balance.—The approximate distribution of the absorbed oxygen is expressed in the following Table, 93% of the oxygen being accounted for:

	H_2O				(KS)	Residue
Proportion of O_2 absorbed (wt. %) ...	25	23	10	8	22	5

Dimethyl disulphide was formed to the extent of 0·12 mole/mole of oxygen absorbed.

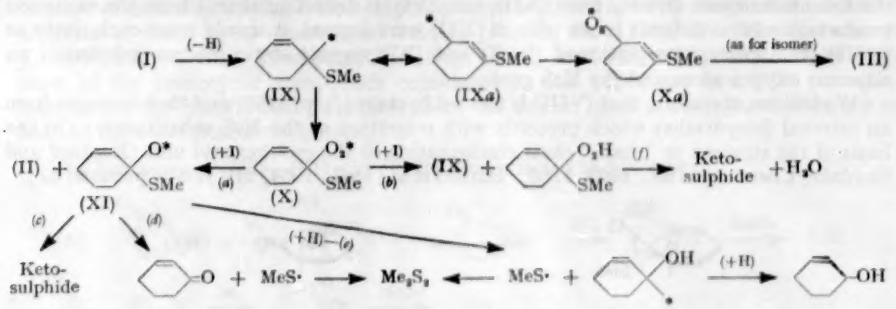
Course of the Reaction.—In view of the complexity of the products and the inference that several alternative or consecutive reactions must be occurring during the oxidation, consideration of the reaction mechanism is limited to developing a reasonable working picture on which to base further experiments.

The general features of the oxidation of allylic sulphides described in Part III lead to two important conclusions. First, the marked catalysis by thermally decomposing azo*iso*butyronitrile and by ultraviolet irradiation and the inhibition by quinol and similar compounds show that the primary attachment of oxygen involves free-radical intermediates. Secondly, the fact that oxygen absorption proceeds initially much faster than with a comparable olefin, coupled with the high reactivity of cinnamyl phenyl sulphide, points to the CH or CH_2 group activated by both the double bond and the sulphur atom being the primary reactive centre. In addition, very little polymeric product is formed (p. 2002), thus showing the unimportance of attack by peroxy-radicals at the double bond and of the following sequence of reactions:

$$RO_2\cdot + C{:}C \longrightarrow RO_2{\cdot}C{\cdot}C\cdot \xrightarrow{O_2} RO_2{\cdot}C{\cdot}C{\cdot}O_2\cdot \xrightarrow{C{:}C}$$

$$RO_2{\cdot}C{\cdot}C{\cdot}O_2{\cdot}C{\cdot}C\cdot \xrightarrow{O_2} \textit{etc.}$$ (cf. Bateman, *Quart. Rev.*, 1954, **8**, 147).

The annexed scheme is based on these features.

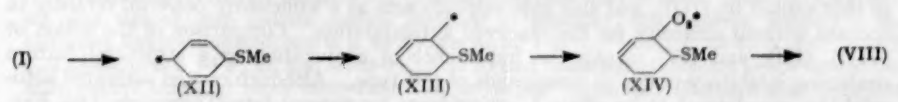


The finding of roughly equal molar proportions of (II), *cyclo*hexenone and *cyclo*hexenol together, keto-sulphide, and water indicates, on this scheme, that reactions (*a*) and (*b*) proceed with equal facility and that reaction (*c*) is negligible. These are not unreasonable consequences.

Hydroperoxides appear to react with allylic sulphides in aprotic solvents, not molecularly as in alcohols to give sulphoxides in quantitative yield, but probably *via* radicals to give only fractional yields of sulphoxides (Barnard, unpublished results; see Parts I and II, *Proc. Roy. Soc.*, 1954, *A*, **224**, 389, 399). Hydrogen abstraction by peroxy-radicals, as invoked in step (*b*), is the fundamental basis of numerous other autoxidations, but the oxygen-transfer process (*a*) has only recently been recognized (Part II). The reactions of (XI) expressed in (*d*) and (*e*) simulate the behaviour of the formally similar *tert.*-alkoxy-radicals derived from di-*tert.*-butyl peroxide and *tert.*-butyl hydroperoxide (see Bell, Raley, Rust, Seubold, and Vaughan, *Discuss. Faraday Soc.*, 1951, **10**, 242). These oxy-radicals show no tendency to oxidize sulphides to sulphoxides in the manner of their peroxy-counterparts (Barnard, unpublished results).

While it is difficult to envisage the transformation of (XI) into a keto-sulphide, the reaction path (IX) ⟶ (IX*a*) ⟶ (X*a*) would be expected to give (III). Although spectroscopic evidence points to the presence of (III) in the keto-sulphide mixture, the amount is so small that neither the liquid ketone nor its crystalline derivatives have been separated and characterized. This is a peculiar feature because 1 : 4-dienes undergo double-bond displacement on autoxidation to give the completely conjugated hydroperoxide : C:C·CH·C:C ⟶ C:C·C:C·C(O_2H) (Bateman, *loc. cit.*), and similar behaviour might have been expected in the present system in view of the considerable conjugation between a double bond and an adjacent sulphur atom (Koch, *J.*, 1949, 387), as shown chemically, for example, in the tendency of allylic sulphides to isomerize into vinylic sulphides on heating (Tarbell and McCall, *J. Amer. Chem. Soc.*, 1952, **74**, 48). Further, whatever the relative importance of the mesomeric structures (IX) and (IX*a*), steric factors would be expected to cause the latter to be the preferred configuration on reaction with other molecules.

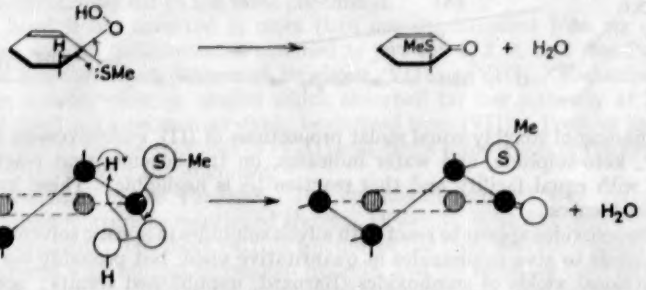
In contrast to the above, a double-bond displacement or an equivalent process is clearly involved in the formation of the main keto-sulphide (VIII). The simplest explanation is that hydrogen abstraction from the sulphide (I) occurs at the non-sulphurated allylic position, followed by reaction of the resulting radical in the isomeric form :



but this seems unlikely for two reasons. First, the increased oxidizability of the *cyclo*hexenyl unit produced by the MeS substituent cannot reasonably be associated with increased reactivity at a methylene group essentially unaffected by the substituent, *i.e.*,

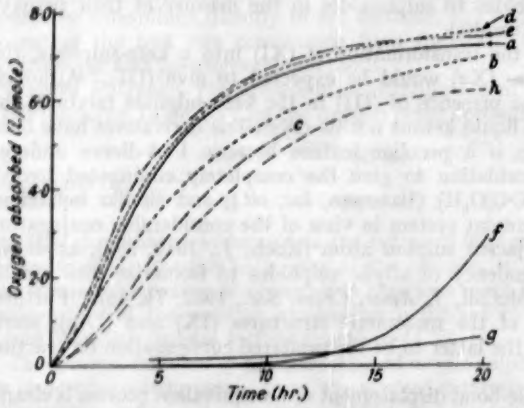
it is difficult to believe that the proportion of (XII) to (XI) can be appreciable. Secondly, the ketone derivable directly from (XII), *viz.*, (VI), is definitely absent from the oxidation products, and it is difficult to see why, if (XII) were formed, it should react exclusively as (XIII) [the spectral properties of (VIII) and (VI) suggest steric hindrance between an adjacent oxygen atom and the MeS group].

We believe, therefore, that (VIII) is formed in stage (*f*) (p. 1999) and that it results from an internal dehydration which proceeds with migration of the MeS substituent. On the basis of the strained or " half " chair configuration of the *cyclo*hexenyl unit (Raphael and Stenlake, *Chem. and Ind.*, 1953, 1286; Barton *et al.*, *ibid.*, 1954, 21), this is pictured as :



Somewhat similar and unusual bond displacements, which scale models show to be quite feasible sterically, are encountered with *cyclo*hexenyl hydroperoxide itself, *e.g.*, in the acid-catalysed dehydration to *cyclo*pentenaldehyde.

The chain character of the autoxidation, which is revealed by the response to catalyst and inhibitors (Part III), originates in the operation of reactions (*b*) and possibly (*e*) (p. 1999).



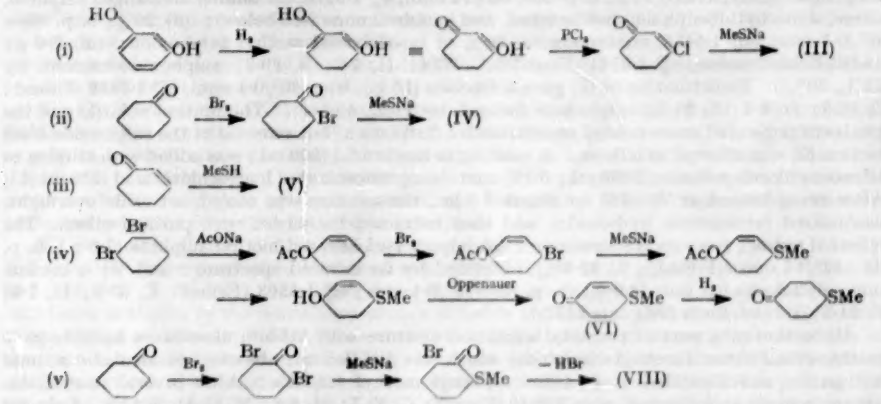
Effect of the reaction products and some keto-sulphides on the autoxidation of cyclohexenyl methyl sulphide at 55°.

a, (I) alone; *b*, (I) + H_2O (11·8% molar); *c*, (I) + (II) (4·5% molar); *d*, (I) + (V) (1·6% molar); *e*, (I) + *cyclo*hexenone (6·3% molar); *f*, (I) + (III) (5·4% molar); *g*, (I) + (VIII) (5·4% molar); *h*, (I) + dimethyl disulphide (3·2% molar).

Influence of the Reaction Products on Autoxidation.—The effect of additions of (II), (VIII), *cyclo*hexenone, water, and dimethyl disulphide on oxygen uptake by the sulphide (I) is shown in the Figure. Only (VIII) has any significant effect [which is closely similar to that caused by (III)], and this keto-sulphide acts as a sufficiently powerful retarder to account without difficulty for the observed autoinhibition. Comparison of the action of (VIII), (III), and (IV) reveals the importance of conjugation as a structural feature conferring inhibitory power on compounds of this type. Although certain saturated keto-sulphides are claimed to be efficient antioxidants for natural fats (Thompson, *Ind. Eng. Chem.*, 1951, **43**, 1638; 1952, **44**, 1659), the inactivity of (IV) in the present system parallels the small effect of 4-ethylthiobutan-2-one on the oxidation of *n*-butyl cinnamyl sulphide (Part III, *loc. cit.*).

Synthesis and Properties of the Keto-sulphides prepared for Comparison.—Although a number of saturated aliphatic keto-sulphides have been prepared by the general method of addition of thiols to αβ-unsaturated ketones (Posner, *Ber.*, 1902, **35**, 809; Ruhemann, *J.*, 1905, **87**, 17, 461; Thompson, *Ind. Eng. Chem.*, 1951, **43**, 1638; U.S.P. 2,492,334), most of the homocyclic compounds considered in this paper are new. Of particular interest are the unsaturated examples where the double bond is conjugated with one or both of the other functional groups.

The syntheses of (III)—(VI) and (VIII) were effected as follows:



Certain characteristic properties of these keto-sulphides and their derivatives are summarized in Table 1.

TABLE 1.

	Keto-sulphide				2:4-Dinitrophenylhydrazone			Semicarbazone		
Compound	n_D^{20}	ν_{CO} [1] (cm.$^{-1}$)	$\lambda_{max.}$ (Å)	ε [2]	M. p.	$\lambda_{max.}$ (Å)	ε [2]	M. p.	$\lambda_{max.}$ (Å)	ε [2]
(IV)	1·5115	1708	2530	497	137—138°	2540	12,310	171—172°	2300	14,270
			3040	315		3630	22,600			
			3030	922 *		3500 (infl.)				
(V)	1·5172	1715	2630	339	148	3630	24,050	165	2310	13,130
			2880	45·5						
p-O:C$_6$H$_4$·SMe	—	—	—	—	145—146	3620	22,800	—	—	—
(VI)	1·5487	1690	—	—	146—147	2500	17,780	156—160	—	—
						3740	28,260			
(VIII)	1·5608	1690	3000	4,250	234	3750	26,700	234	2650	17,440
(III)	1·5902	1655	2870	20,800	212	2650	14,750	207—208	2930	34,030
						3020	12,850			
						4000	30,250			

[1] For neat liquids. [2] In ethanol, except for * in aqueous 2N-NaOH.

EXPERIMENTAL

Microanalyses were carried out under the direction of Dr. W. T. Chambers.

cyclo*Hex*-2-*enyl Methyl Sulphide*.—3-Bromo*cyclo*hexene (Ziegler *et al.*, *Annalen*, 1942, **551**, 80) was treated with sodium methyl sulphide in ethanol; the *sulphide*, isolated in the usual way and fractionated, had b. p. 64·5°/14 mm., n_D^{20} 1·5210 (Found: C, 65·5; H, 9·4; S, 25·1. $C_7H_{12}S$ requires C, 65·6; H, 9·4; S, 25·0%). It formed trimethylsulphonium iodide on reaction with methyl iodide at room temperature. The derived sulphoxide (Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 476) had b. p. 75°/0·1 mm., n_D^{20} 1·5384 (Found: C, 58·1; H, 8·5; S, 22·3. Calc. for $C_7H_{12}OS$: C, 58·3; H, 8·4; S, 22·2%).

To test the effect of the alkyl substituent on oxidizability (see Part III), the following *cyclo*hex-2-enyl sulphides were prepared analogously: *ethyl*, b. p. 76°/14 mm., n_D^{20} 1·5140 (Found:

C, 67·5; H, 9·9; S, 22·7. $C_8H_{14}S$ requires C, 67·5; H, 9·9; S, 22·5%); *isopropyl*, b. p. 84°/14 mm., n_D^{20} 1·5062 (Found: C, 68·8; H, 10·4; S, 20·4. $C_9H_{16}S$ requires C, 69·1; H, 10·3; S, 20·5%); *tert.-butyl*, b. p. 97°/14 mm., n_D^{20} 1·5015 (Found: C, 70·5; H, 10·7; S, 18·4. $C_{10}H_{18}S$ requires C, 70·5; H, 10·7; S, 18·8%); *phenyl*, b. p. 77°/0·1 mm., n_D^{20} 1·5929 (Found: C, 75·4; H, 7·2; S, 16·9. $C_{12}H_{14}S$ requires C, 75·8; H, 7·4; S, 16·8%).

Oxidation Procedure.—The sulphide, kept at 55°, was shaken without solvent in purified oxygen supplied from a constant-temperature and -pressure gas-burette, mercury (which behaves as silicone oil for this sulphide, cf. Part III, *loc. cit.*) being used as the manometric fluid.

Separation of Oxidation Products by Distillation.—The oxidized sulphide (**103 g.**, containing 7·3 g. of oxygen) gave (i) **73** g., b. p. 60—65°/14 mm., n_D^{20} 1·5170, containing unchanged sulphide, water, dimethyl disulphide, *cyclo*hexenol, and *cyclo*hexenone (see below); (ii) **20** g., b. p. 80—90°/0·1 mm., n_D^{20} 1·5435, containing *ca.* 50% of *cyclo*hexenyl methyl sulphoxide; (iii) 7·6 g., undistillable residue, n_D^{20} 1·5744 (Found: C, 57·4; H, 7·2; S, 20·2; sulphoxide content, by $TiCl_3$, 30%). Redistillation of (ii) gave a fraction (15 g.), b. p. 80°/0·1 mm., n_D^{20} 1·5468 (Found: C, 58·6; H, 8·1; S, 21·2; sulphoxide content, by $TiCl_3$, 49·5%). The mutual volatility of the products prevented more refined separation by distillation, but removal of the sulphoxide from faction (ii) was effected as follows. A solution in acetic acid (900 ml.) was added with stirring to titanous chloride solution (2430 ml.; 0·1N) containing concentrated hydrochloric acid (150 ml./l.). After being heated at 70—75° for about 2·5 hr., the solution was cooled, set aside overnight, neutralized (ammonium hydroxide), and then extracted for 48 hr. with purified ether. The ethereal extract gave on fractionation: (*a*) impure *cyclo*hexenyl methyl sulphide (7·0 g.), b. p. 65—67°/14 mm. (Found: S, 22·8%), identified by its infrared spectrum; and (*b*) a ketonic non-sulphoxylic fraction (8·0 g.), b. p. 67—70°/0·1 mm., n_D^{20} 1·5503 (Found: C, 57·9; H, 7·4; S, 24·3%), henceforth designated (KS).

Reduction of a part of the total oxidation mixture with lithium aluminium hydride gave methanethiol (from dimethyl disulphide) which was distilled off, absorbed in alcoholic sodium hydroxide, and identified as 2 : 4-dinitrophenyl methyl sulphide. After several recrystallisations from ethanol this had m. p. 126·5° (Found: C, 39·3; H, 2·8; N, 13·4; S, 14·8. Calc. for $C_7H_6O_4N_2S$: C, 39·3; H, 2·8; N, 13·2; S, 15·0%).

Chromatographic Separation.—Silica gel (200 mesh) was used as adsorbent (decomposition occurred on alumina). All solvents were redistilled immediately before use, the methanol from magnesium methoxide. Oxidized sulphide (11·0 g.) in light petroleum (b. p. <40°; 650 ml.) was passed down the column (45 × 2 cm.), followed by: (1) light petroleum (1250 ml.); (2) light petroleum–10% ether (100 ml.); (3) light petroleum–20% ether (2250 ml.); (4) light petroleum–50% ether (800 ml.); (5) ether (400 ml.); (6) methanol (230 ml.). All eluates were concentrated by carefully evaporating the solvents through a Fenske column. Fraction (1) consisted of the parent sulphide and dimethyl disulphide; (2)—(5) contained *cyclo*hexenol, *cyclo*hexenone, and ketonic sulphides; (6) gave *cyclo*hexenyl methyl sulphoxide, n_D^{20} 1·5374, identified by direct comparison with an authentic specimen (Barnard and Hargrave, *loc. cit.*). Fractions (2)—(5) were combined and fractionated at 0·1 mm. The components volatile at room temperature were *cyclo*hex-2-enol (α-naphthylurethane, m. p. and mixed m. p. with authentic specimen 150—151°) and *cyclo*hex-2-enone (2 : 4-dinitophenylhydrazone, m. p. and mixed m. p. with authentic specimen, 159—160°); the remainder consisted of a fraction virtually identical with (KS), b. p. *ca.* 70°/0·1 mm., and a small non-distillable residue.

Properties and Characterization of (KS).—(*A*) Warming with 2 : 4-dinitrophenylhydrazine in aqueous hydrochloric acid gave a crystalline precipitate, m. p. 168—180°. The heterogeneity of this derivative was clearly shown by paper chromatography (chloroform being used as the stationary phase on acetylated paper), elution by methanol–water (85 : 15) giving two spots, one weak with R_F 0·38 the other strong with R_F 0·19. The first simulates the behaviour of the 2 : 4-dinitrophenylhydrazones of the saturated keto-sulphides (IV) and (V); the second that of the differently conjugated derivatives from (III) and (VI). Fractional crystallization gave a small proportion of red needles (from pyridine–light petroleum), m. p. 148—149° (Found: C, 48·4; H, 4·8; N, 17·2; S, 9·4. $C_{13}H_{16}O_4N_4S$ requires C, 48·2; H, 5·0; N, 17·3; S, 9·9%), having $\lambda_{max.}$ 3670 Å, $E^{1\%}_{1\,cm.}$ 714; the parent saturated keto-sulphide has not been identified. The main constituent, later shown to be derived from the compound (VIII), formed dark red needles from pyridine–ethanol or benzene, m. p. 235°, $\lambda_{max.}$ 3750 Å, $E^{1\%}_{1\,cm.}$ 787 (Found: C, 48·5; H, 4·4; N, 17·5; S, 9·7. $C_{13}H_{14}O_4N_4S$ requires C, 48·4; H, 4·4; N, 17·4; S, 9·9%).

The *semicarbazone* of the main constituent of (KS) had m. p. 236°, $\lambda_{max.}$ 2650 Å, $E^{1\%}_{1\,cm.}$ 865 (Found: C, 48·3; H, 6·5; N, 21·1; S, 16·1. $C_9H_{13}ON_5S$ requires C, 48·2; H, 6·6; N, 21·1; S, 16·1%).

(*B*) The infrared absorption of (KS) indicated the presence of three types of carbonyl grouping: (*a*) an αβ-unsaturated ketone showing strong absorption at 1690 cm.$^{-1}$; (*b*) <5% contained in the more strongly conjugated grouping S–C=C–C=O, absorbing at 1656 cm.$^{-1}$; (*c*) a minor amount of a saturated ketone absorbing at 1708 cm.$^{-1}$. The ultraviolet spectrum showed broad maximal absorption at 2850—3050 Å ($E^{1\%}_{1\,cm.}$ 290).

(*C*) The material (KS) (1·2 g.) was heated at 75—80° with Raney nickel (catalyst "C"; Hurd and Rudner, *J. Amer. Chem. Soc.*, 1951, **73**, 5157) in ethanol solution (50 ml.) with continuous stirring under a stream of nitrogen for 3 hr. The mixture was filtered, the nickel thoroughly extracted with boiling ethanol, and the combined liquors concentrated to about 15 ml. This solution was shaken in hydrogen over palladium–charcoal: no hydrogen was absorbed. The product was isolated in the usual way and distilled (0·7 g.), n_D^{20} 1·4600 (authentic *cyclo*hexanol, n_D^{20} 1·4643). It readily formed an α-naphthylurethane, m. p. and mixed m. p. with a specimen prepared from *cyclo*hexanol, 125—126°. In a trial experiment, 3-methylthio-*cyclo*hex-2-enone (III) gave *cyclo*hexanol in similar yield.

(*D*) Hydrogenation of (KS) over palladium–charcoal (hydrogen absorption, 0·85 mole), and distillation gave a product consisting largely of 2-methylthio*cyclo*hexanone (IV), n_D^{20} 1·5200, and having an infrared spectrum nearly identical with that of a synthetic specimen. This compound was definitely absent before hydrogenation. The orange 2 : 4-dinitrophenylhydrazone could not be obtained pure by crystallization, and had a m. p. several degrees lower than the derivative prepared from the synthetic keto-sulphide.

(*E*) Reduction of (KS) (0·6 g.) with lithium aluminium hydride (0·1 g.) in dry ether (10 ml.), and isolation of the product in the usual way, gave a liquid (0·35 g.), n_D^{20} 1·5650 (Found: C, 56·5; H, 7·7; S, 24·4%). The small amount of (III) originally present appeared to remain unreduced as shown by the non-disappearance of bands at 1655 and 1570 cm.$^{-1}$, but the absence of absorption at 1690 cm.$^{-1}$ (due to unsaturated carbonyl grouping) showed that reduction of the main constituent was complete. The ultraviolet spectrum was consistent with the latter conclusion (weak absorption at 2900 Å), the relatively weak absorption at 2300 Å proving the absence of vinylic sulphide grouping C=C–S. There is very strong absorption in the 3-μ region. The compound is impure 6-methylthio*cyclo*hex-2-enol.

Synthesis of 6-Methylthiocyclohex-2-enone (VIII) *and its Identification as the Main Component of* (KS).—Methyl sodium sulphide solution prepared from sodium (4·0 g.) and excess of methanethiol was added very slowly with vigorous stirring to 2 : 6-dibromo*cyclo*hexanone (46 g., m. p. 107°; Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 3297) in dry methanol at room temperature. After the addition was complete, the solution was warmed to 50° for 1 hr., then concentrated under reduced pressure, the sodium bromide filtered off, and finally the solvent removed. Attempts to distil the residue led to its decomposition. The crude material was therefore debrominated by treatment with potassium hydroxide (9·0 g.) in ethanol (90 ml.), first at room temperature (3 hr.), then by warming to the b. p. The solution was cooled and filtered, and the solvent removed under reduced pressure. Fractionation of the residue gave *6-methylthiocyclohex-2-enone* (15 g.), b. p. 76—78°/0·1 mm., n_D^{20} 1·5608 (Found: C, 58·9; H, 7·1; S, 22·0. $C_7H_{10}OS$ requires C, 59·1; H, 7·1; S, 22·5%). The 2 : 4-*dinitrophenylhydrazone*, recrystallized from pyridine–ethanol and benzene, formed dark red needles, m. p. 234° (Found: C, 48·3; H, 4·4; N, 17·0; S, 9·7. $C_{13}H_{14}O_4N_4S$ requires C, 48·4; H, 4·4; N, 17·4; S, 10·0%). The *semicarbazone* had m. p. 234° (Found: C, 48·1; H, 6·6; N, 21·1; S, 16·1. $C_8H_{13}ON_3S$ requires C, 48·2; H, 6·6; N, 21·1; S, 16·1%).

The properties of (KS) and (VIII) are compared in Table 2.

TABLE 2.

	KS:		
	Bulk	Main component	(VIII)
n_D^{20}	1·5503	—	1·5608
$\lambda_{max.}$, $E^{1\%}_{1\,cm.}$	2850—3050 Å, 290	—	3000 Å, 299
Carbonyl absorption (cm.$^{-1}$)	1690, 1655, 1708	—	1690
2 : 4-Dinitrophenylhydrazone: m. p.	168—180°	235°	234°
2 : 4-Dinitrophenylhydrazone: $\lambda_{max.}$, $E^{1\%}_{1\,cm.}$	3700 Å, 719	3750 Å, 821	3750 Å, 829
Semicarbazone: m. p.	219—222°	236°	234°
Semicarbazone: $\lambda_{max.}$, $E^{1\%}_{1\,cm.}$	2650 Å, 815	2650 Å, 865	2650 Å, 877

Quantitative Estimation of Oxidation Products.—(A) *Sulphoxide.* This was estimated directly on the total oxidation mixture by Barnard and Hargrave's method (*Analyt. Chim. Acta*, 1951, **5**, 536), and was always within close limits, *viz.*, 23—25% of the oxygen absorbed.

(B) *Water.* This was also estimated on the total oxidation mixture by Karl Fischer's procedure, the usual rigorous precautions to exclude the intrusion of extraneous moisture being observed. The oxidized mixture was washed from the oxidation vessel into a distillation flask with methanol (2—4 ml.) followed by benzene (30—40 ml.). The water–benzene azeotrope was distilled off through a twisted gauze column with a head designed to minimize condensation, and collected in a cooled receiver. The water in the distillate was estimated by electrometric titration with the usual reagents (Fischer, *Z. angew. Chem.*, 1935, **48**, 394). Blank titrations were performed on the solvents. Control experiments with unoxidized sulphide, sulphoxide (dried by azeotropic removal of water with benzene), and a weighed amount of water gave results consistently high by 3·6 mg. after allowance for the solvent blank. Results:

O_x absorbed (mole/mole)	0·28	0·35	0·34	0·32	0·16	0·16
H_xO (mg.) (corr.)	7·8	11·8	11·0	6·5	5·7	7·3
Absorbed O_x found as water (wt. %)	18·7	25·6	25·8	18·0	25·1	30·7

(C) *Dimethyl disulphide.* This was estimated (*a*) by reduction to the thiol and (*b*) polarographically. (*a*) Fraction (i) of the total oxidation mixture (p. 2002) in tetrahydrofuran was dried and reduced with excess of lithium aluminium hydride in ether. Careful addition of cold ethanol and 2N-sulphuric acid gave methanethiol, which was estimated by passage into standard cupric acetate solution, the excess of cupric salt being measured iodometrically (Ellis and Barker, *Analyt. Chem.*, 1951, **23**, 1777). Sulphide (5·55 g.) containing oxygen (0·26 mole/mole) gave dimethyl disulphide (0·14 g.). (*b*) Polarographic estimation on the total oxidation mixture was impossible owing to interference by the relatively large amount of sulphoxide. A polarogram of the fraction used in (*a*) in 85% acetone-free methanol–15% water containing 0·1M-lithium chloride at a dropping-mercury cathode gave a wave of height equal to the sum of those due to dimethyl disulphide and *cyclo*hexenone. The wave height, obtained by subtraction of that due to *cyclo*hexenone [see D (*b*)], corresponded to dimethyl disulphide (0·12 g.).

Estimation of the remaining products was carried out on the appropriate fraction from the chromatographic separation described above, the *cyclo*hexenone and *cyclo*hexenol being contained in the more volatile part of the fractions (2)—(5) (p. 2002).

(D) cyclo*Hex-2-enone.* This was estimated (*a*) spectroscopically and (*b*) polarographically. (*a*) Comparison of intensity of absorption at 1688 cm.$^{-1}$ (conjugated carbonyl) with that of the pure ketone gave a content of 0·29 g., representing 10·3% of the total oxygen absorbed. (*b*) Comparison of the wave, given in 85% acetone-free methanol–15% water containing an acid buffer (HCl and NaOAc) with that of the pure ketone gave a *cyclo*hex-2-enone content of 0·28 g., representing 9·8% of the total oxygen absorbed. Polarographic estimation directly on the more volatile part of the total oxidation mixture [fraction (i), p. 2002] gave a value of 8·2% of the total oxygen absorbed.

(E) cyclo*Hex-2-enol.* Estimation of the intensity of the OH stretching frequency in the 3-μ region gave an approximate value of 0·22 g., representing 7·9% of the total oxygen absorbed.

(F) *Keto-sulphide.* Infrared and ultraviolet examination showed this fraction to have an almost identical composition with that of fraction KS, accounting for 22% of the total oxygen absorbed.

(G) *Involatile residue* (0·14 g.) not identified (Found: O, by diff., 15%), corresponding to 4·5% of the total oxygen absorbed.

Syntheses of Keto-sulphides.—(1) 2-*Methylthio*cyclo*hexanone* (IV). Crude 2-bromo*cyclo*hexanone (12·5 g.; b. p. 55—60°/0·1 mm.) (Found: Br, 43·7. Calc. for C_6H_9OBr: Br, 45·1%), prepared by Kötz's method (*Annalen*, 1908, **358**, 194), in ether (20 ml.) was added slowly with stirring to a solution of methyl sodium sulphide (from 1·64 g. of sodium) in methanol (30 ml.) at 0°. After being warmed to room temperature, the mixture was refluxed for a few minutes, and then worked up in the usual way. The required *keto-sulphide* (3 g.) had b. p. 51°/0·1 mm., n_D^{20} 1·5115 (Found: C, 57·5; H, 8·2; S, 21·8. $C_7H_{12}OS$ requires C, 58·3; H, 8·4; S, 22·2%).

(2) 3-*Methylthio*cyclo*hexanone* (V). *cyclo*Hex-2-enone (5·0 g., prepared by oxidation of *cyclo*hexene with chromic anhydride; cf. Whitmore and Pedlow, *J. Amer. Chem. Soc.*, 1941, **63**, 758), piperidine (0·5 g.), and dry benzene (20 ml.) were mixed in a Carius tube into which methanethiol (3·5 ml.) was then distilled. After being sealed, the tube was heated at 55° for 5 hr. Fractionation of the product gave 3-*methylthio*cyclo*hexanone* (V) (4·5 g.), b. p. 55°/0·1 mm., n_D^{20} 1·5172 (Found: C, 58·7; H, 8·5; S, 21·7. $C_7H_{12}OS$ requires C, 58·3; H, 8·4; S, 22·2%).

(3) 4-*Methylthio*cyclo*hex-2-enone* (VI).—1-Acetoxy-4-bromo*cyclo*hex-2-ene (65·7 g.; Ziegler

et al., loc. cit.) in ethanol (100 ml.) was added slowly to a solution of methyl sodium sulphide (from 6·9 g. of sodium) at room temperature. The mixture was refluxed for 30 min., most of the alcohol then distilled off, and 1-acetoxy-4-methylthio*cyclo*hex-2-ene (46 g.), b. p. 67°/0·1 mm., n_D^{20} 1·5375, isolated in the usual manner. Hydrolysis of this compound with sodium hydroxide in ethanol gave 4-*methylthio*cyclo*hex-2-enol* (28 g.), b. p. 65—67°/0·1 mm., n_D^{20} 1·5468 (Found: C, 58·2; H, 8·2; S, 22·1. $C_7H_{12}OS$ requires C, 58·3; H, 8·4; S, 22·2%), which on Oppenauer oxidation and careful fractionation of the product gave 4-*methylthio*cyclo*hex-2-enone* (4·0 g.), b. p. 60°/0·1 mm., n_D^{20} 1·5489 (Found: C, 59·2; H, 7·3; S, 22·6. $C_7H_{10}OS$ requires C, 59·1; H, 7·1; S, 22·5%).

Hydrogenation of this keto-sulphide over palladium–charcoal gave impure 4-methylthio-*cyclo*hexanone, which formed an orange-yellow 2 : 4-*dinitrophenylhydrazone* (from light petroleum–ethanol), m. p. 145—146° (Found: C, 48·3; H, 5·2; N, 17·1. $C_{13}H_{16}O_4N_4S$ requires C, 48·2; H, 5·0; N, 17·3%).

(4) 3-*Methylthio*cyclo*hex-2-enone* (III).—Dihydroresorcinol, m. p. 98°, obtained by hydrogenation of resorcinol over Raney nickel (*Org. Synth.*, 1943, **27**, 21), was converted into 3-chloro*cyclo*hex-2-enone (b. p. 78°/14 mm., n_D^{20} 1·5204. Found: Cl, 27·2. Calc. for C_6H_7OCl: C, 55·2; H, 5·4; Cl, 27·2%) by treatment with phosphorus trichloride in chloroform (see Crossley and Haas, *J.*, 1903, **83**, 498). This chloro-compound (8·2 g.) in benzene (10 ml.) was added to a suspension of methyl sodium sulphide in benzene (obtained by saturating methanol containing sodium with methanethiol and then changing the solvent by distillation and simultaneous addition of benzene) at 0° with vigorous stirring. After 1 hr., the mixture was heated to 70—80° for 0·5 hr., cooled, and poured into water. Ether-extraction and subsequent fractionation gave 3-*methylthio*cyclo*hex-2-enone* (5·0 g.), b. p. 75°/0·1 mm., n_D^{20} 1·5902 (Found: C, 59·0; H, 7·0; S, 22·4. $C_7H_{10}OS$ requires C, 59·1; H, 7·1; S, 22·5%).

We are indebted to Dr. D. E. Bethell, Mr. G. Higgins, and Dr. E. S. Waight for the spectroscopic data, and to them and Drs. D. Barnard and J. I. Cunneen for advice and criticism throughout the course of this work.

British Rubber Producers Research Association,
Tewin Road, Welwyn Garden City, Herts. [*Received, November 26th*, 1954.]

The Constitution of Yeast Ribonucleic Acid. Part XVI. The Nature of Methylated Yeast Ribonucleic Acid and its Stability to Alkalis.*

By G. R. Barker, T. M. Noone, Miss M. A. Parsons, Miss L. Pickstock, and D. C. C. Smith.

[Reprint Order No. 6125.]

Previous evidence for the existence of a branched structure in yeast ribonucleic acid has been re-examined and earlier conclusions are withdrawn. Evidence is presented in support of current views regarding the alkaline hydrolysis of ribopolynucleotides.

A previous communication (Anderson, Barker, Gulland, and Lock, *J.*, 1952, 369) described the methylation of yeast ribonucleic acid and the hydrolysis of the product to yield ribose and mono- and di-*O*-methylriboses. On the basis of these results a structure was put forward involving branching of the polynucleotide chain, but it was pointed out that the validity of the conclusions depended on three assumptions: first, that the unsubstituted ribose does not arise through failure to methylate all available hydroxyl groups; secondly, that dimethylriboses are not produced from simple nucleotides formed by degradation of the polynucleotide; thirdly, that the mixture of carbohydrates analysed is representative of the carbohydrate residues in the methylated polynucleotide. Almost simultaneously with the publication of this work, Brown and Todd (*J.*, 1952, 52) put forward an explanation of the alkaline lability of ribopolynucleotides which materially affected the reliability of conclusions drawn from methylation experiments. Considerable discussion of the question

* Part XV, *J.*, 1952, 369.

of branching has since taken place (Brown and Todd, *loc. cit.*; Brown, Magrath, and Todd, *J.*, 1954, 1442; Markham and Smith, *Biochem. J.*, 1952, **52**, 558; Cohn, Doherty, and Volkin in "Phosphorous Metabolism, Vol. II," The Johns Hopkins Press, 1952, p. 345; Cohn and Volkin, *J. Biol. Chem.*, 1953, **203**, 319) and further work has therefore been carried out to test the previous conclusions.

Methylation of adenosine-3′ phosphate by the technique previously described gave a product which, after hydrolysis with acid, yielded ribose, mono-, di-, and tri-*O*-methylriboses and a considerable quantity of material which remained on the starting line in paper chromatograms. The last fraction, which probably consists of sugar phosphate derivatives, will be referred to later. The mono- and di-*O*-methylribose fractions were examined by paper chromatography in butanol–boric acid (Barker and Smith, *Chem. and Ind.*, 1954, 19; Barker, Noone, Smith, and Spoors, *J.*, 1955, 1327) and were found not to be homogeneous. The mono-*O*-methylribose fraction was most convenient for study and was shown to consist of 2-, 3-, and 5-*O*-methyl-D-ribose. These results were in apparent agreement with those obtained by Brown, Magrath, and Todd (*loc. cit.*) for the methylation of uridine-3′ phosphate. However, since tri-*O*-methylribose was present, it was clear that dephosphorylation had occurred, and therefore it cannot be concluded from the heterogeneity of the methylated riboses that migration of the phosphate group had taken place during methylation. The methylated adenylic acid was therefore subjected to a brief treatment with aqueous alkali and that part of the methylated product which had suffered dephosphorylation was removed by chromatography on Dowex-1 resin. That part which still retained the phosphoryl residue was hydrolysed with acid and the methylated riboses were examined as before and again found not to be homogeneous. This indicates conclusively that the phosphate ester group migrates during the methylation. It follows that in these circumstances methylation cannot distinguish between a 2′- and a 3′-phosphate ester grouping. It is also clear that, since methylation of adenylic acid is incomplete and is accompanied by some dephosphorylation, the first two assumptions quoted above require further consideration.

In the previous work, the extent of the methylation was assessed on the basis of the methoxyl content of the product, and in view of the fact that nucleosides were readily methylated, it was considered that methylation of the nucleic acid was substantially complete. It must be borne in mind, however, that the observed methoxyl content could have arisen by some residues being undermethylated and others overmethylated after degradation. In view of the results now reported with adenylic acid, the presence of ribose in the hydrolysate of methylated nucleic acid does not necessarily indicate branching of the polynucleotide chain.

The degree to which degradation occurs during the methylation of a polynucleotide is more difficult to assess than in the case of a simple nucleotide. Further, no simple method exists for separating degraded and undegraded material such as was used with methylated adenylic acid. In the previous experiments, the crude methylated nucleic acid was fractionated by solvent precipitation and the diffusion coefficient of the isolated material was compared with that of the original nucleic acid. This gives an average value for the molecular size and since the yeast ribonucleic acid used as starting material was undoubtedly polydisperse, the question of the homogeneity of the product does not merit consideration. As far as is known, the only ribonucleic acid which has been claimed to be homogeneous was prepared by relatively strong alkaline treatment of yeast (Jungner and Allgén, *Acta Chem. Scand.*, 1950, **4**, 1300). This treatment is likely to affect the internucleotide linkages and it was considered undesirable to use material prepared in this way. Thus, although determination of molecular weight is the most convenient method of determining the extent of degradation in the methylated polynucleotide, it is possible that the uncertainty arising from the polydispersity of the materials makes it insufficiently sensitive for the present purpose. It was therefore decided to seek further evidence of degradation.

There is now considerable evidence for the existence of ester linkages between positions 3′ and 5′ in adjacent nucleotides of ribonucleic acids. It follows that if the mono- and di-*O*-methylribose fractions represent corresponding structural units in the original polynucleotide as previously assumed, 2-*O*-methyl-D-ribose (and 3-*O*-methyl-D-ribose owing to

phosphoryl migration) is to be expected in the mono-*O*-methylribose fraction, but no appreciable quantity of 5-*O*-methyl-D-ribose. Examination of the mono- and di-*O*-methylribose fractions by chromatography in butanol–water and in butanol–boric acid (Barker and Smith, *loc. cit.*; Barker, Noone, Smith, and Spoors, *loc. cit.*) showed that 2-, 3-, and 5-*O*-methyl-D-ribose and 2 : 5-, 2 : 3-, and 3 : 5-di-*O*-methyl-D-ribose were present. This random distribution of the methyl groups strongly suggests that the mono-*O*-methylribose fraction arose, not only from a methylated polynucleotide chain, but also by partial methylation of fragments. It follows that the di-*O*-methylribose fraction may have arisen in a similar way and may not solely represent end groups in the polynucleotide. It seems likely, however, in view of the average molecular weights obtained by diffusion measurements, that degradation was not extensive in spite of the uncertainties mentioned above. In that case, it appeared probable that the small yield of methylated riboses obtained from the methylated product was derived mostly from small fragments rather than from the large undegraded molecules. It was, therefore, desirable to reconsider the third assumption, namely, that the sample of sugars examined was representative.

With this object in view, attempts have been made to increase the yield of methylated riboses. Although some success has been achieved, it has been impossible to obtain a recovery of more than approximately 40%. The reason for this is that in the methylated polynucleotide the phosphoryl linkages are much more stable to hydrolysis than those in the original molecule and this is believed to be because methylation of carbohydrate hydroxyl groups prevents the formation of cyclic phosphates as postulated by Brown and Todd (*loc. cit.*). It is also relevant that after hydrolysis of methylated adenylic acid, a phosphorus- and carbohydrate-containing spot was observed on the starting line in paper chromatograms and this also is believed to be due to the same effect. It is interesting that Levene and Harris (*J. Biol. Chem.*, 1932, **98**, 9) observed that a phosphoryl residue in methylated methyl riboside was resistant to hydrolysis.

From the above considerations it is concluded (*a*) that methylation cannot be used to locate a phosphoryl residue on the 2- or 3-position of ribose, (*b*) that methylation of yeast ribonucleic acid previously reported was probably incomplete, (*c*) that the methylated product contained some degraded material, and (*d*) that, owing to the stability of the phosphate ester linkages in the methylated product, the small yield of sugars obtained was not a representative sample. The last is believed to be the most important factor, since it will tend to exaggerate the effects due to (*b*) and (*c*). The authors are of the opinion that, within the limits imposed by factor (*a*) above, the technique of methylation could be applied successfully to the study of polynucleotides if a method were found for recovering all the carbohydrate residues from the methylated products. With this object in view, and also in order to provide further support for Brown and Todd's theory, a detailed study was made of the hydrolysis of methylated yeast ribonucleic acid.

The rates of mineralisation of the phosphate of yeast ribonucleic acid and methylated yeast ribonucleic acid by hot dilute acid are shown in Fig. 1. Hydrogenation (cf. Levene and LaForge, *Ber.*, 1912, **45**, 608; Levene and Jorpes, *J. Biol. Chem.* 1929, **81**, 575), and treatment with bromine (cf. Gurin and Hood, *J. Biol. Chem.*, 1941, **139**, 775; Massart and Hoste, *Biochim. Biophys. Acta*, 1947, **1**, 83) or with hydrazine (cf. Levene and Bass, *J. Biol. Chem.*, 1926—7, **71**, 167; Caputto, Leloir, Cardini, and Paladini, *ibid.*, 1950, **184**, 333) before acid hydrolysis did not materially affect the rate of mineralisation. The highest recovery was obtained when the methylated polynucleotide was subjected first to alkaline and then to acid hydrolysis. The course of the alkaline hydrolysis was therefore studied further.

In order to determine the rate of the alkaline hydrolysis of the internucleotide linkages of the methylated nucleic acid, the following procedure was adopted. At intervals during the hydrolysis, the number of equivalents of acid liberated (primary and secondary phosphate dissociations) and the number of mols. of free methanol were determined. The difference between these figures gives a value for the number of sugar–phosphate linkages broken. Aliquot parts of the hydrolysate were also neutralised and treated with prostate phosphomonoesterase and the free phosphate was determined. This gave a value for the number of monoester groups produced by the alkaline cleavage and it was found that this

equalled the number of sugar–phosphate bonds broken. It follows that in the initial rapid fission of triester residues, methanol alone is split off. Since, as can be seen from Fig. 1, little or no mineralisation of phosphate occurs, measurements of the monoester residues produced, or of the sugar–phosphate linkages broken, give the rate of fission of the internucleotide linkages in the methylated nucleic acid. A comparison of the stability of the original nucleic acid and the methylated product is shown in Fig. 2, and it is seen that fission is much slower in the methylated material. In order to confirm that this is due to the blocking of hydroxyl groups adjacent to phosphoryl residues, a similar study has been made of a specimen of yeast ribonucleic acid methylated with diazomethane, kindly supplied by Professor J. K. N. Jones. This material contained methoxyl groups attached to phosphorus, but, after hydrolysis, yielded a large quantity of ribose and only a trace of

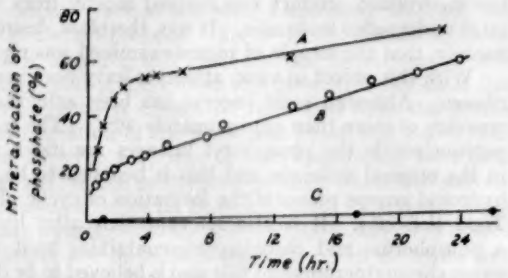


FIG. 1. *Mineralisation of phosphate.*

A, Yeast ribonucleic acid in 0·5N-sulphuric acid at 95°.
B, Methylated (MeI–Ag_2O) yeast ribonucleic acid in 0·5N-sulphuric acid at 95°.
C, Methylated nucleic acid (as for *B*) in 0·5N-sodium hydroxide at 37°.

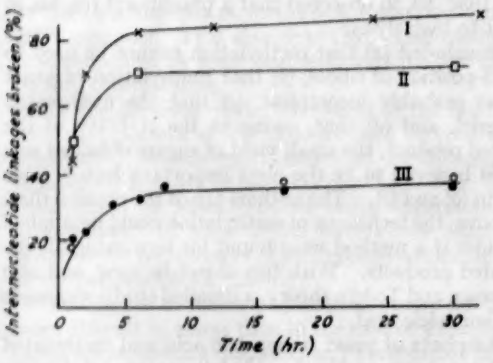


FIG. 2. *Fission of internucleotide linkages by 0·5N-sodium hydroxide.*

I, Yeast ribonucleic acid (determined by titration).
II, Yeast ribonucleic acid methylated by diazomethane (determined enzymically).
III, Yeast ribonucleic acid methylated by methyl iodide and silver oxide.

● Calc. from titration and determination of methanol.
○ determined enzymically.

methylated sugars. This indicated that, for the most part, hydroxyl groups adjacent to phosphoryl residues are not substituted. Comparison of this material with nucleic acid methylated with methyl iodide and silver oxide (see Fig. 2) indicates that the former product is more readily hydrolysed by alkali. All these considerations provide further confirmation of Brown and Todd's views.

EXPERIMENTAL

Methylation of Adenosine-3′ Phosphate.—Adenosine-3′ phosphate (0·23 g.) was methylated as previously described (Anderson *et al.*, *loc. cit.*), nine additions of silver oxide and methyl iodide being made. Removal of solvent under reduced pressure below 60° gave a pale yellow glassy product (0·26 g.) (Found: OMe, 25·0. Calc. for $C_{14}H_{21}O_4N_5$: OMe, 27·6%).

Hydrolysis of Methylated Adenosine-3′ Phosphate.—The above methylated adenylic acid in 0·5N-sodium hydroxide (45 c.c.) was kept at 37° for 17 hr. The solution was adjusted to pH 7·1 by addition of glacial acetic acid, diluted to 1750 c.c. (optical density 1·15 at 260 mμ), and run on to a column (12 × 5 cm.) of Dowex-1 resin (200—400 mesh) in the chloride form.

The column was washed with distilled water and the combined effluents (2315 c.c.; optical density 0·5 at 260 mμ) were rejected. The resin was then eluted with N-hydrochloric acid, and the fraction (732 c.c.; optical density 0·96 at 260 mμ) was collected. This solution (or, in experiments in which alkaline hydrolysis was omitted, a solution of methylated nucleotide in N-hydrochloric acid) was refluxed for 2 hr. and, after being cooled, adjusted to pH 6·9 by addition of sodium hydroxide solution. The solution was concentrated under reduced pressure to dryness, the residual solid which contained much sodium chloride was extracted repeatedly with hot methanol, and the combined extracts (300 c.c.) were again concentrated to dryness. The residue was dissolved in water (25 c.c.) and passed first through a column (10 × 1·5 cm.) of Amberlite IR-120 resin in the hydrogen form and then through a column (10 × 1·5 cm.) of Amberlite IRA-400 resin in the hydroxide form. The resulting solution was evaporated under reduced pressure to a very small volume and was applied to a sheet of Whatman No. 1 filter-paper and chromatographed with *n*-butanol–water. The paper was then dried and sprayed with saturated aqueous boric acid, care being taken to avoid wetting the original chromatographic lane. The paper was then chromatographed in *n*-butanol–boric acid in a direction at right angles to the original direction, dried, and sprayed with aniline phthalate. Besides a spot corresponding in position to D-ribose, faint spots were obtained in the region expected for dimethylriboses, but they were not strong enough to allow of identification with certainty. Discrete spots were obtained, however, which correspond in R_F value with 2-, 3-, and 5-*O*-methyl-D-ribose.

Examination of the Carbohydrate Residues of Methylated Yeast Ribonucleic Acid.—The methylated nucleic acid (Anderson *et al.*, *loc. cit.*) (0·65 g.) in 0·5N-sodium hydroxide (50 c.c.) was kept at 37° for 14 hr. N-Sulphuric acid (25 c.c.) was added and, after being diluted to 780 c.c. and made 0·5N with respect to sulphuric acid, the solution was kept at 95—100° for 1·5 hr., cooled, and passed through a column (11 × 3 cm.) of Amberlite IR-120 resin (hydrogen form) and then through a column of Amberlite IR-4B (carbonate form). The total effluent was concentrated under reduced pressure to a syrup which was found by the method of Hirst, Hough, and Jones (*J.*, 1949, 928) to contain 0·09 g. of reducing sugar expressed as ribose. Two-dimensional paper chromatography by the method described above gave spots corresponding to ribose and 2-, 3-, and 5-*O*-methyl-D-ribose. Also, three spots of approximately equal intensity were present corresponding to 2 : 3-, 2 : 5-, and 3 : 5-di-*O*-methyl-D-ribose. The mono-*O*-methylribose fraction was also examined by chromatography on a column of Dowex-1 in the borate form. Elution with 0·01M-sodium tetraborate gave three well-defined fractions, detected colorimetrically by a modification of A. H. Brown's method (*Arch. Biochem.*, 1946, 11, 269) and shown to contain 2-, 3-, and 5-*O*-methyl-D-ribose by comparison on paper chromatograms in *n*-butanol–boric acid with synthetic material (Barker, Noone, Smith, and Spoors, *loc. cit.*).

Rate of Liberation of Acid Groups by Alkaline Hydrolysis.—Measurements were made during the hydrolysis of yeast ribonucleic acid, of yeast ribonucleic acid methylated with methyl iodide and silver oxide, and of yeast ribonucleic acid methylated with diazomethane. The following is a typical experiment. The results are shown in Fig. 1.

Aliquot parts (2 c.c.) of a solution of methylated ribonucleic acid (0·42 g.) in water (25 c.c.) were maintained at 37° with N-sodium hydroxide (2 c.c.) in stoppered tubes. At intervals, tubes were opened, N-sulphuric acid (2 c.c.) was added and, after dilution to approximately 35 c.c., the solutions were titrated electrometrically with 0·1N-sodium hydroxide. It is assumed that at pH 7·5 primary and secondary phosphoric acid dissociations have been titrated (cf. Fletcher, Gulland, and Jordan, *J.*, 1944, 33).

Liberation of Methanol during the Alkaline Hydrolysis of Methylated Ribonucleic Acids.—Methylated nucleic acid (0·28 g.) in 0·5N-sodium hydroxide (25 c.c.) was kept at 37°. At intervals, aliquot parts (2 c.c.) were withdrawn and, after being adjusted to pH 7 by the addition of 0·5N-hydrochloric acid, the solutions were diluted to 30 c.c. and methanol was determined colorimetrically (Hoffpauir and O'Connor, *Analyt. Chem.*, 1949, 21, 420). Results are shown in Fig. 1.

Formation of Monoester Residues during the Alkaline Hydrolysis of Methylated Ribonucleic Acids.—Methylated nucleic acid (0·114 g.) in 0·5N-sodium hydroxide 10 c.c.) was kept at 37° for 47 hr. An aliquot part (5 c.c.) of the hydrolysate was brought to pH 5·1 by the addition of N-sulphuric acid and diluted to 50 c.c. Two aliquot parts (1 c.c. each) were used for the determination of total phosphorus (Allen, *Biochem. J.*, 1940, 34, 858), and the rest of the solution was divided into two halves. To one half was added water (1 c.c.) and to the other was added a solution (1 c.c.) of prostate phosphomonoesterase (Beale, Harris, and Roe, *J.*, 1950, 1397). Both solutions were incubated at 37° and, after varying intervals of time, aliquot parts (3 c.c.) were removed and free phosphate was determined (Allen, *loc. cit.*). The final constant value

gave the number of singly esterified phosphoryl residues in the hydrolysate. The whole experiment was repeated with various times of hydrolysis with sodium hydroxide. Results are shown in Fig. 2.

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*The Kinetics of Alkyl–Oxygen Fission in Ester Hydrolysis. Part II.** tert.-*Butyl* 2 : 4 : 6-*Trimethylbenzoate in Aqueous Acetone.*

By V. R. STIMSON.

[Reprint Order No. 5937.]

The kinetics of the acid-catalysed hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate have been studied in acetone–water mixtures at various acid concentrations and at three temperatures, and in acetone–ethanol mixtures at 97°. The Arrhenius equation is accurately followed, and the values of E and A are significantly different from those found in ester hydrolysis with acyl–oxygen fission. The variation of rate with solvent composition is discussed in terms of proton-availability.

COHEN and SCHNEIDER (*J. Amer. Chem. Soc.*, 1941, **63**, 3382) have shown that *tert.*-butyl 2 : 4 : 6-trimethylbenzoate is readily hydrolysed in acidic aqueous and alcoholic media and have proved that alkyl–oxygen fission is involved in alcoholysis. Stimson and Watson (Part I *) have shown that the kinetics of the acid-catalysed hydrolysis in aqueous ethanol display features not usually found in ester hydrolysis with acyl–oxygen fission. The hydrolysis has now been studied in aqueous acetone.

EXPERIMENTAL

Acetone (2 l.) was refluxed with potassium permanganate until the pink colour remained, distilled, dried (K_2CO_3), and distilled, the first 100 c.c. being rejected ; the fraction used had b. p. 53·3°/680 mm., n_D^{18} 1·3598. The experimental procedure has been described (Part I, *loc. cit.*). All runs (except *a*, *b*, *c*, and *d*) gave integrated first-order rate constants ($\overline{k_1}$) (Bateman, Hughes, and Ingold, *J.*, 1940, 963) that agreed to *ca.* 1 part in 50 parts.

As previously noted by Church and Hughes (*J.*, 1940, 920), the acid titre decreased when hydrochloric acid was heated in acetone containing only small quantities of water. The decrease per hour was found to be *ca.* 1% of the titre in 98% acetone at 97° for 0·01N-solutions. With benzenesulphonic acid, however, the titre after 15 hr. under the same conditions agreed to 1 part in 200 parts with the initial titre.

RESULTS AND DISCUSSION

The hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate in aqueous acetone accurately follows first-order kinetics (except in cases *a*, *b*, *c*, and *d*) (see Table 1) and the rate constants (k_1) are independent of the ester concentration and proportional to the acid-catalyst concentration, which is in accordance with the kinetic requirements of the proposed mechanism $A''1$ (Part I, *loc. cit.*).

The Arrhenius equation $k_1/c_A = A_{Arr.} \exp(-E_{Arr.}/RT)$ is obeyed in 60% acetone where $E_{Arr.} = 30{\cdot}5 \pm 0{\cdot}5$ kcal./mole, $\log_{10}A_{Arr.}$ (sec.$^{-1}$) = 16·1, and $\Delta S_{97}^{\ddagger}$ (cf. Part I) = 12 cal. mole^{-1} deg.$^{-1}$. In 80% acetone these values are 31·0 kcal./mole, 16·2, and 13 cal. mole^{-1} deg.$^{-1}$, respectively. The value of $\log_{10}(10^6 k_1/c_A)$ (k_1 in sec.$^{-1}$) is 4·1 (calc.) at 100°

* Part I, *J.*, 1954, 2848.

in 60% aqueous acetone, this rate being more than 100 times that of the hydrolysis of ethyl esters of nine substituted benzoic acids in the same solvent (Timm and Hinshelwood, *J.*, 1938, 862).

It is clear from its high rate that this reaction is not sterically hindered. In general, the rate of hydrolysis is not very different from that in aqueous ethanol of comparable composition. The activation energy is again of the order of 30 kcal./mole, which is quite different from that for acid-catalysed hydrolysis involving acyl–oxygen fission in this

TABLE 1. *First-order rate constants (k_1) for the hydrolysis of* tert.*-butyl 2 : 4 : 6-trimethylbenzoate.*

(c_A and c_E are the concentrations, in moles/l., of acid catalyst and ester, respectively.)

Solvent : Acetone–water.

$COMe_2$ (% by vol.)	Temp.	10^2c_A	10^2c_E	10^3k_1 (min.$^{-1}$)	$10k_1/c_A$ *
60	97·2°	2·00	1·73	11·9	5·9
,,	,,	1·52	1·27	8·6	5·6
,,	,,	1·10	1·13	6·4	5·8
,,	,,	0·72	1·35	4·2	5·8
,,	84·3	1·06	1·41	1·56	1·28
,,	72·3	2·39	2·30	0·68	0·285
80	97·2	1·09	1·46	4·4	4·0
,,	84·3	1·11	1·71	0·96	0·86
90	97·1	1·13	1·31	3·9	3·5
95	97·2	1·15	1·33	2·9 [a]	2·5
96	97·2	1·62	1·60	3·4 [c]	2·1
98	97·2	1·89	1·75	2·2 [d]	1·2

Solvent : Acetone–ethanol. [e]

$COMe_2$ (% by vol.)	10^2c_A	10^2c_E	Temp. 97·2° 10^3k_1 (min.$^{-1}$)	$10k_1/c_A$ *
0	0·56	1·47	9·7	17·1
10	0·51	1·45	8·2	16·1
20	0·55	1·27	7·6	13·8
40	0·54	1·85	7·2	13·3
60	0·52	1·70	6·5	12·4
80	0·54	1·51	5·8	10·7
90	0·55	1·78	5·6 [b]	10·2

(*a*), (*b*), (*c*), (*d*). In solvent mixtures less aqueous than 90% acetone and with hydrochloric acid as catalyst the reaction did not follow the simple first-order equation, the rate falling as the reaction proceeded. For (*a*) and (*b*) $\bar{k}_1^{(0\cdot5)}/k_1^{(0)} = 0{\cdot}9$, and for (*c*) and (*d*) 0·7 and 0·6. The value of $k_1^{(0)}$ was obtained by extrapolation to zero time. The cause of the fall in rate in (*a*), (*c*), and (*d*) is largely the loss of hydrochloric acid by reaction with acetone. (*e*) Benzenesulphonic acid was used as catalyst (cf. Part I). The reaction in this solvent is $C_6H_2Me_3{\cdot}CO_2Bu^t + HOEt \longrightarrow C_6H_2Me_3{\cdot}CO_2H + Bu^tOEt$.

* In units min.$^{-1}$ l. mole^{-1}.

solvent (Timm and Hinshelwood, *loc. cit.*; Davies and Evans, *J.*, 1940, 339; Smith and Steele, *J. Amer. Chem. Soc.*, 1941, **63**, 3466). The values of $A_{Arr.}$ and $\Delta S_{97}^{\ddagger}$ are comparable with those found in aqueous ethanol (Part I).

As in aqueous ethanol (Part I) $\log_{10} k_1/c_A = mD + n$ for 60—90% acetone (cf. Fig. 1). The value of m (0·016) is independent of temperature. In 60 and 80% acetone, $\Delta E_D = 1{\cdot}7$ and 1·4 kcal./mole, respectively.

The mechanism $A''1$ proposed in Part I is consistent with the demonstration that racemisation occurs in the acid-catalysed hydrolysis of the acetate of the tertiary alcohol *iso*hexylethylmethylcarbinol (3 : 7-dimethyloctan-3-ol) in 70% aqueous acetone at 76° (Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **166**, 680). They found k_1/c_A to be $6{\cdot}2 \times 10^{-1}$ min.$^{-1}$ l. mole^{-1}, which is 20 times the rate for *tert.*-butyl 2 : 4 : 6-trimethylbenzoate interpolated from the present results. The relation between these two rates is of the expected kind and order of magnitude.

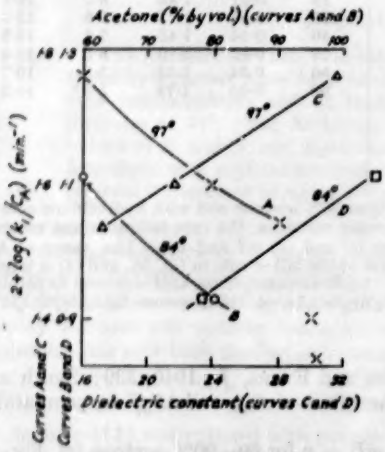
TABLE 2. *First-order rate constants for the hydrolysis at 97° and the H function for the solvent.* [a]

Aqueous ethanol. [b,c]				Aqueous acetone.			
EtOH (%)	$\log_{10} k' - H$	EtOH (%)	$\log_{10} k' - H$	$COMe_2$(%)	$\log_{10} k' - H$	$COMe_2$(%)	$\log_{10} k' - H$
60	0·8	90	0·6	60	0·9	90	0·9
70	0·7	100	1·8	80	1·0	95	0·5
80	0·7						

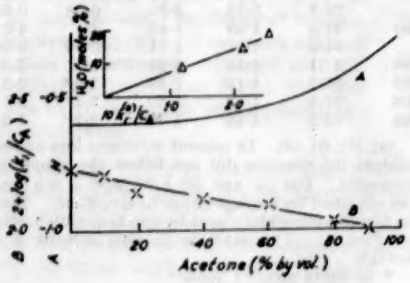
[a] The H function is that of Braude (*J.*, 1948, 1971) and is the negative of the Hammett acidity function. An increase in H corresponds to an increase in the protonating power of the solvent. No values of H for 0·01M-hydrogen chloride in the mixed solvents are available but from the relation between H and c_A it seems likely that the H–solvent composition curves for 0·01M- and 0·1M-hydrogen chloride will be parallel; the values of H were taken as one unit less than those of 0·1M-hydrogen chloride (Braude and Stern, *J.*, 1948, 1976). [b] From Part I. [c] k' is the rate constant interpolated for 0·0100M-hydrogen chloride.

Since primary alkyl esters of 2 : 4 : 6-trimethylbenzoic acid are hydrolysed only with difficulty in aqueous or alcoholic solvents it appears unlikely that hydrolysis with acyl–oxygen fission, *i.e.*, by mechanism $A_{Ac}2$, occurs at an appreciable rate in any esters of this acid, this mechanism being influenced more strongly by the acid than the alcohol portion of the ester. In non-aqueous solvents acyl–oxygen fission would lead to trans-esterification, in the present case by the reaction $C_6H_2Me_3{\cdot}CO_2Bu^t + HOEt \longrightarrow C_6H_2Me_3{\cdot}CO_2Et + Bu^tOH$, no acid being produced. Cohen and Schneider (*loc. cit.*) found that 10% of 2 : 4 : 6-trimethylbenzoic acid was produced in methanolysis, and in the present case, where the initial quantity of ester was measured by weighing and the reaction followed by titrating the acid produced; good first-order constants were obtained throughout the reaction in ethanol and ethanol–acetone, so that the reaction must occur almost entirely by alkyl–oxygen fission in these solvents. The rate shows that hydrolysis by this mechanism is not unusually difficult; the mechanism should be available in aqueous solvents and the similar rate supports this contention.

FIG. 1.



FIGS. 2 and 3 (inset).



Variation of Rate with Solvent Composition.—For the proposed mechanism (Part I) variations of rate with solvent composition may occur in the protonating (step 1) and the bond-breaking (step 2) process. The effect in the former may be considered by the method that Braude and Stern (*J.*, 1948, 1982) have used in the case of anionotropic rearrangement. The values of ($\log_{10} k' - H$) (Table 2) are reasonably constant for solvent mixtures containing up to 90% of the organic component. Protonation of esters is not likely to vary in exactly the same way as that of the nitroanilines with which H was measured, so that $\log_{10} k' - H$ cannot be expected to be strictly constant, and it is noteworthy that the same kind of small variation in $\log_{10} k' - H$ found by Braude and Stern (*loc. cit.*) for the alcohols is found in the present case. They showed that a constant difference between $\log_{10} k'$ and H is evidence that the protonation step is fast.

In the limited range of solvents used (those containing 60—90% of ethanol or acetone) variations in rate may be accounted for by a consideration of step 1, so that the effect due to step 2 is probably small. In less aqueous solvents other considerations become necessary as is shown by a number of features.

(i) Although in 100% ethanol the rate is 5 times that in 90% ethanol (Part I), yet it is only *ca.* 1/10 of that expected from a consideration of H alone (cf. Table 2). No such discrepancy is observed in anionotropic rearrangements in which the slow second step is internal (Braude and Stern, *loc. cit.*; Braude, *J.*, 1948, 794). In the present case the solvent, especially when of low water content, is likely to have a significant effect on the second step, the production of a molecule and an ion.

(ii) In aqueous acetone containing more than 90% of acetone the rate decreases (cf. Fig. 1) although the *H* function rises steeply; in fact for more than 95% of acetone the rate is roughly proportional to the amount of water present (Fig. 3), which is like the behaviour of S_N1 reactions (Bateman, Cooper, and Hughes, *J.*, 1940, 913).

It is suggested that as long as the solvating power of the solvent remains high owing to considerable water content, the variation of rate with solvent composition is determined largely by the protonating power of the medium, but when this is not so the power of the solvent to assist the second step becomes the determining factor.

Some confirmation of this is afforded by the rate in ethanol–acetone mixtures where the *H* function shows no minimum but rises steadily with increasing acetone content (Braude and Stern, *loc. cit.*); the rate falls, however, approximately linearly with the ethanol content (Fig. 2).

The author thanks Dr. N. V. Riggs for discussion.

NEW ENGLAND UNIVERSITY,
ARMIDALE, N.S.W., AUSTRALIA.

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The Action of Grignard Reagents on Anhydro-sugars of Ethylene Oxide Type. Part IV. The Behaviour of Methyl 2 : 3-Anhydro-4 : 6-O-benzylidene-α-D-mannoside towards Diphenylmagnesium.*

By G. N. RICHARDS.

[Reprint Order No. 6045.]

Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside with diphenylmagnesium in ether gives methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside. In boiling toluene the same reagent also causes racemisation of the benzylidene group. Theories of the reactions of Grignard reagents with epoxides are discussed.

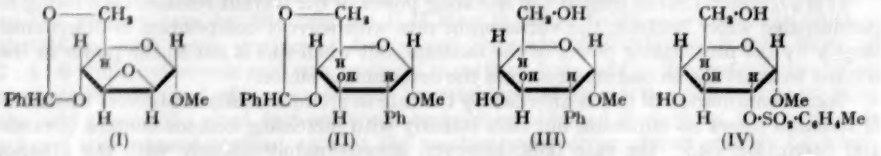
IN Part III* reference was made to the reaction of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I) with diphenylmagnesium and it was pointed out that the nature of the product, methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (II), indicated a different direction of ring opening from the corresponding reaction with diethylmagnesium (Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308). We now report a more detailed study of the former reaction.

Treatment of the anhydro-mannoside (I) with ethereal phenylmagnesium iodide, from which the whole of the iodine had been precipitated as the dioxan complex (cf. Schlenk, *Ber.*, 1931, **64**, 734), followed by fractionation, yielded as sole product methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (II) (m. p. 163·5°). The structure of this compound was demonstrated by its partial acidic hydrolysis to methyl 2-deoxy-2-*C*-phenyl-α-D-glucoside (III), which reacted with 1 equivalent of lead tetra-acetate at a rate corresponding to the presence of a *trans*-α-glycol group. For comparison, methyl 2-*O*-toluene-*p*-sulphonyl-α-D-glucoside (IV) was prepared from its known 4 : 6-*O*-benzylidene derivative (Bollinger and Prins, *Helv. Chim. Acta*, 1945, **28**, 465) and shown to react with lead tetra-acetate in an analogous manner. The ultraviolet absorption spectrum confirmed the presence of a phenyl group in (III) and, if the assumption made in earlier papers of this series concerning the absence of rearrangement reactions, is accepted, its structure must be considered proved.

When the reaction with diphenylmagnesium was repeated under more drastic conditions, in boiling toluene solution for 3 or 6 hours, two compounds isomeric with (II) were also obtained (m. p. 144·5° and m. p. 194·5°). These compounds, which will be referred to as methyl 4 : 6-*O*-benzylidine-2-deoxy-2-*C*-phenyl-α-D-glucoside (A) and (B) respectively, differed in melting point and to a smaller extent in optical rotation from (II), but showed

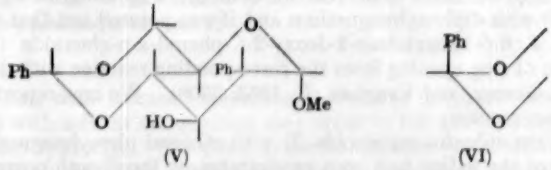
* Part III, *J.*, 1954, 4511.

the same ultraviolet absorption spectrum and on partial acidic hydrolysis gave the same product (III); the differences in optical rotation of the hydrolysed solutions are probably due to the presence of optically active hemiacetals of benzaldehyde. It is concluded that compounds (A) and (B) are stereoisomeric with (II), differing only at the optical centre



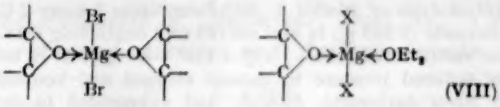
(I) (II) (III) (IV)

introduced by the benzylidene group, and the optical activities indicate that (A) may be the racemate of (II) and (B). The behaviour of these compounds on recrystallisation, and in particular the difficulty experienced in obtaining a sample of sharp melting point from compound (A), is reminiscent of the results of Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1946, **68**, 1769; 1948, **70**, 765) with benzylidene derivatives of heptitols, but the racemisation of the glucoside derivatives seems to take place much less readily than with 1 : 3-*O*-benzylideneglycerol (Irvine, Macdonald, and Souter, *J.*, 1915, **107**, 344). This fact is rather unexpected, since in only one of the stereoisomers (V) is the bulky phenyl of the benzylidene group in the equatorial configuration, and the alternative form (VI) would be expected to be relatively unstable. Accordingly this type of isomerisation in the pyranoside series is normally found only in 5-membered benzylidene rings, such as methyl 2 : 3-4 : 6-di-*O*-benzylidene-α-D-mannoside (cf. Mills, *Chem. and Ind.*, 1954, **633**), where the two forms do not differ greatly in stability. The racemisation would be assisted by the basic character of the diphenylmagnesium (cf. Ness, Hann, and Hudson, *loc. cit.*; Buchanan, *Chem. and Ind.*, 1954, 1484) and possibly also by the presence of the phenyl anion formed from it on ionisation. Racemisation by pyridine is demonstrated by its use as solvent in the benzoylation of the compound (II), yielding an ester which was purified with difficulty and on hydrolysis yielded compound (B). This suggests that the ease of racemisation may depend on the presence of the phenyl group in the pyranoside ring.



(V) (VI)

The above results serve to emphasise the fact that in a Grignard reagent solution where the Schlenk equilibrium renders possible two different types of simple scission of an epoxide ring, the normal ring opening agent is MgX_2, while the products arising from reaction of MgR_2 are observed only when MgX_2 is removed from solution, *e.g.*, as the dioxan complex. This may perhaps be explained as due to the more complete ionisation of the magnesium halide as compared with the di-alkyl- or -aryl-magnesium, since the anion (X^- or R^-) would be the agent involved in attack on the carbon atoms of the epoxide ring. Or alternatively the greater polarity of the Mg–X bond compared with the Mg–R bond may assist complex formation in the former case and hence cause preferential reaction. Either of these possibilities would explain the increased reactivity of diphenyl- as compared with diethylmagnesium (cf. Foster *et al.*, *loc. cit.*), and in addition the results of Johnson and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 1943) indicate that the concentration of the former will be the greater. In this connection Huston and Agett's isolation (*J. Org. Chem.*, 1941, **6**, 123) of the complex $C_4H_8O_2MgBr_2$ in the reaction of ethylene oxide with alkylmagnesium bromides is of interest and indicates that a complex of type (VII) or possibly (VIII) (cf. Part I, *J.*, 1950, 2356) is the reactive intermediate in this type of reaction, theoretically capable of *trans*-addition of either halide or alkyl anion (cf. Angyal, *Chem. and Ind.*, 1954, 1230).



(VII) (VIII)

The isolation of the stereoisomers described above must render less conclusive the tentative assignment of structure made in Part III of this Series (*loc. cit.*) to the supposed methyl 4 : 6-*O*-benzylidene-2-deoxy-2-iodo-α-D-glucoside.

Experimental

Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside was prepared by the method of Bollinger and Prins (*loc. cit.*).

Reaction of Methyl 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside with Diphenylmagnesium.*—(a) *In ether.* To the Grignard reagent prepared from iodobenzene (5·57 ml.) and magnesium (1·2 g.) in ether (20 ml.), dioxan (6 ml.) was added dropwise with stirring, and the resulting paste treated with a solution of the anhydro-sugar (1·36 g.) in ether (125 ml.). Thereafter the mixture was heated under reflux with vigorous stirring for 10 hr. and kept at room temperature for a further 12 hr. Water was next added cautiously, followed by a slight excess of dilute hydrochloric acid, the ether layer separated, and the aqueous phase further extracted with ether. The combined ethereal extracts were washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated to dryness. The partly crystalline residue (3·80 g.) was shaken at room temperature with ether (10 ml.) and light petroleum (5 ml.; b. p. 60—80°), the unchanged anhydromannoside (0·281 g.; m. p. and mixed m. p. 146—147°) remaining undissolved. The solution was then transferred to alumina (30 × 1 cm.) and eluted as follows: (i) Ether–light petroleum (b. p. 60—80°) (2 : 1) gave a colourless optically inactive liquid, which, when distilled at 115—120° (bath-temp.)/18 mm., yielded crystalline diphenyl, m. p. 68—70° (Found: C, 92·9; H, 6·3. Calc. for $C_{12}H_{10}$: C, 93·5; H, 6·5%). (ii) Further use of the same eluant yielded the unchanged anhydro-sugar (0·734 g., total recovery 74%) showing m. p. and mixed m. p. 146—147° when once recrystallised from ethanol. (iii) Elution with chloroform yielded methyl 4 : 6-O-*benzylidene*-2-*deoxy*-2-*C*-*phenyl*-α-D-*glucoside* (0·345 g., 19%), which, when recrystallised twice from benzene–light petroleum (b. p. 60—80°), had m. p. 162·5—163·5°, $[\alpha]_D^{21}$ +143° (*c*, 1 in $CHCl_3$) (Found: C, 69·9; H, 6·3. $C_{20}H_{22}O_5$ requires C, 70·1; H, 6·5%). Ultraviolet absorption: ε 506 at 2150 Å, 495 at 2550 Å.

(b) *In toluene.* The reagent was prepared in ether exactly as in the previous experiment. Ether was next removed from the resulting paste by slow distillation with vigorous stirring, while toluene (50 ml.) was slowly added. After the complete removal of ether, a solution of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (1·37 g.) in toluene (25 ml.) was added and the mixture heated under reflux with vigorous stirring for 6 hr. The product, isolated as in the previous experiment, crystallised partly and the crystals when separated on sintered glass and recrystallised from light petroleum (b. p. 60—80°) had m. p. 162—163° alone or in admixture with the product from the previous experiment (0·80 g.). The remaining syrup was dissolved in light petroleum (5 ml.; b. p. 60—80°), transferred to alumina (30 × 1 cm.), and eluted as follows: (i) Ether–light petroleum (b. p. 60—80°) (2 : 1) yielded needles mixed with a liquid. The crystals, when separated on sintered glass, were methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (B) (0·183 g., 10%), and when once recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) had m. p. 193·5—194·5°, $[\alpha]_D^{19}$ +126° (*c*, 1 in $CHCl_3$) (Found: C, 69·9; H, 6·6%). Ultraviolet absorption, ε 498 at 2150 Å, 5·21 at 2550 Å. The liquid filtrate distilled at 115—120° (bath-temp.)/18 mm. to yield diphenyl (2·23 g.), m. p. and mixed m. p. 68—70°. (ii) Elution with chloroform yielded a further quantity of methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (0·34 g., total yield 64%).

A further experiment under conditions similar to (b) above, except that the reaction mixture was heated for only 3 hr., yielded, after chromatography on alumina, diphenyl (2·90 g.) and compound (B) (0·09 g., 5%), but later fractions gave in addition, methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (A) (1·60 g., 91%), m. p. 139—145°. Recrystallisation of this product from ethanol resulted in more diffuse m. p.s, but after several recrystallisations from benzene–light petroleum and later from ethyl acetate–light petroleum it had m. p. 144—144·5°, $[\alpha]_D^{22}$ + 132° (*c*, 1 in $CHCl_3$) (Found: C, 69·8; H, 6·4%). Ultraviolet absorption, ε 501 at 2150 Å, 521 at 2550 Å. The m. p. of this compound after 3 years was 150—160°.

Partial Acid Hydrolysis of Methyl 4 : 6-O-*Benzylidene*-2-*deoxy*-2-C-*phenyl*-α-D-*glucoside*.—A solution of the glucoside (0·319 g.) in ethanol (25 ml.) containing 0·1N-hydrochloric acid (1 ml.) was heated under reflux for 2·5 hr. $\{[\alpha]_D^{20}$ +119° ⟶ +50·5° (2 hr., const.)$\}$. After steam-distillation under reduced pressure to remove ethanol and benzaldehyde the solution was neutralised with silver carbonate, filtered, and evaporated to dryness. The residue was extracted with boiling light petroleum (5 ml.; b. p. 60—80°), and the insoluble portion recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving *methyl* 2-*deoxy*-2-C-*phenyl*-α-D-*glucoside* as colourless needles, m. p. 180·5—181·5°, $[\alpha]_D^{18}$ +175° (*c*, 0·5 in EtOH) (Found : C, 61·0; H, 7·1. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%). Ultraviolet absorption, ε 507 at 2100 Å, 278 at 2575 Å.

Compound (A) (0·873 g.), treated as in the preceding experiment $\{[\alpha]_D^{18}$ +107° ⟶ +37° (2 hr., const.)$\}$, yielded the same product, m. p. and mixed m. p. 180·5—181·5°. Similar treatment of compound (B) (0·183 g.) in ethanol (12·5 ml.) and 0·1N-hydrochloric acid (0·5 ml.) $\{[\alpha]_D^{16}$ +70° ⟶ +76° (0·5 hr., const.)$\}$ also yielded this product, m. p. and mixed m. p. 180·5—181·5°.

Partial Acid Hydrolysis of Methyl 4 : 6-O-*Benzylidene*-2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside*.—The glucoside (0·494 g.) was heated under reflux for 6 hr. with acetone (25 ml.) and aqueous oxalic acid (0·9 g. of dihydrate in 3 ml.) ($[\alpha]_D$ +51° ⟶ +72°). More oxalic acid (0·9 g.) was added and the whole was heated for 4 hr. ($[\alpha]_D$ ⟶ +80°), and finally 2N-sulphuric acid (2 ml.) was added and the whole heated for a further 3 hr. ($[\alpha]_D$ ⟶ +80°, const.). The solution was distilled in steam to remove benzaldehyde and acetone, and the remaining aqueous solution neutralised with barium carbonate, filtered, and evaporated to dryness. The residue crystallised on trituration with ethyl acetate (0·38 g., 96%) and, when recrystallised from the same solvent, *methyl* 2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside* had m. p. 136—137°, $[\alpha]_D^{20}$ + 81° (*c*, 1 in $CHCl_3$) (Found : C, 48·5; H, 5·7; S, 9·15. $C_{14}H_{20}O_8S$ requires C, 48·2; H, 5·8; S, 9·2%).

Oxidations with Lead Tetra-acetate.—Methyl 2-deoxy-2-*C*-phenyl-α-D-glucoside consumed the following amounts of lead tetra-acetate at room temperature under conditions prescribed by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) : 0·06 equiv./mole (1·5 hr.), 0·36 (44 hr.), 0·54 (66 hr.), 0·78 (111 hr.), 1·01 (242 hr.), 1·07 (336 hr.). The corresponding figures obtained with methyl 2-*O*-toluene-*p*-sulphonyl-α-D-glucoside were : 0·10 (1 hr.), 0·54 (47 hr.), 0·74 (75 hr.), 0·99 (252 hr.), while for comparison methyl 2-deoxy-2-bromo-α-D-altroside has been shown (Part II, *loc. cit.*) to consume 1 equiv. in 0·5 hr.

Methyl 3-O-*Benzoyl*-4 : 6-O-*benzylidene*-2-*deoxy*-2-C-*phenyl*-α-D-*glucoside*.—A solution of methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (88 mg.) in dry pyridine (2 ml.) was treated with benzoyl chloride (0·2 ml.) at room temperature for 2 days. The solution was poured into water, and the product isolated in the usual manner as a yellow oil, which crystallised very slowly on trituration with ethanol–water. When recrystallised several times from the same solvents the 3-O-*benzoyl derivative* had m. p. 102—103° (Found : C, 72·7; H, 5·7. $C_{27}H_{26}O_6$ requires C, 72·6; H, 5·9%).

This material (55 mg.) was hydrolysed by heating it under reflux for 2 hr. with sodium hydroxide (0·1 g.) in ethanol (5 ml.) and chloroform (2 ml.). The resulting suspension was shaken with chloroform (10 ml.) and water (10 ml.), and the aqueous phase further extracted with chloroform. The combined chloroform extracts, after being washed with water saturated with carbon dioxide, were then dried (Na_2SO_4) and evaporated to dryness, to yield methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (B), showing, when recrystallised once from light petroleum, m. p. and mixed m. p. 191—193°.

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The Chemistry Department, The University, Edgbaston, Birmingham 15.
(Present address : The British Rayon Research Association,
Heald Green Laboratories,
Wythenshawe, Manchester.)

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Studies in the Synthesis of Cortisone. Part XI. Infrared Absorption of Alkoxy- and Acetoxy-steroids.*

By J. E. PAGE.

[Reprint Order No. 6134.]

Absorption bands in the 1150—1000-cm.$^{-1}$ region may be used to identify the stereochemical configuration of 3-acetoxy- and 3-methoxy-steroids, the carbon–oxygen stretching frequency for an equatorial bond being slightly greater than that for an axial bond. The ether linkages in a *gem*-dialkoxy-steroid give four carbon–oxygen stretching bands.

FÜRST, KUHN, SCOTONI, and GÜNTHARD (*Helv. Chim. Acta*, 1952, **35**, 951; see also Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571, and Rosenkrantz and Zablow, *ibid.*, 1953, **75**, 903) have shown that in 2-, 3-, and 4-hydroxy-steroids the carbon–oxygen stretching frequency for an equatorial (1044—1037 cm.$^{-1}$) is greater than that for an axial hydroxyl group (1036—996 cm.$^{-1}$), and Corey, Sneen, Danaher, Young, and Rutledge (*Chem. and Ind.*, 1954, 1294) have reported that the stretching frequency for carbon–deuterium and carbon–chlorine linkages is greater for the equatorial than for the axial arrangement. These findings are in harmony with our observations on the infrared absorption of 3-methoxy-steroids and suggest that *in general* the stretching frequency for an equatorial substituent in ring A is probably slightly greater than that for an axial substituent. This hypothesis may be explained qualitatively by an extension of the suggestion advanced for 3-hydroxy-steroids by Cole *et al.* (*loc. cit.*) that the stretching motion of an equatorial 3-substituent causes appreciable expansions and contractions of ring A, whereas the stretching motion of an axial 3-substituent is largely normal to the plane of the ring and will have a smaller effect; the restoring force acting on $C_{(3)}$ should therefore be less for the axial than for the equatorial motion and should induce a lower vibration frequency.

Our hypothesis does not conflict with the observations by Jones, Humphries, Herling, and Dobriner (*J. Amer. Chem. Soc.*, 1951, **73**, 3215) and by Fürst *et al.* (*loc. cit.*) that equatorial 2- and 3-acetoxy-steroids give single peaks and axial 2- and 3-acetoxy-steroids multiple absorption peaks at about 1240 cm.$^{-1}$; 4-acetoxycholestane is exceptional in that both stereoisomers yield complex absorption peaks. Thompson and Torkington (*J.*, 1945, 640) showed that a simple alkyl acetate gives two strong carbon–oxygen stretching bands in the 1250—1000-cm.$^{-1}$ region; the stronger band at about 1240 cm.$^{-1}$ is associated with the carbon–oxygen linkage contiguous to the carbonyl group and the second band at about 1050 cm.$^{-1}$ with the carbon–oxygen linkage of the alcohol residue. It is the absorption frequency for the latter band at about 1050 cm.$^{-1}$ that we should expect to be greater for an equatorial than for an axial acetoxy-group; previously the behaviour of this band has not been studied systematically (see Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252). The band can be readily identified in the spectra of simple steroids and steroidal sapogenins, but its precise frequency cannot always be assigned in the spectra of compounds containing two or more acetate groups and in those of acetoxy-steroids containing hydroxyl groups. The apparent molecular extinction coefficient of the band ranges from about 350 to 200 and is about one-third that of the corresponding 1240-cm.$^{-1}$ band.

An examination of the infrared spectra of the 3-acetoxy-steroids (in CS_2 solution) available to us, of the spectra reproduced by Dobriner, Katzenellenbogen, and Jones ("Infrared Absorption Spectra of Steroids. An Atlas," Interscience Publ. Ltd., London, 1953), and of the absorption frequency values reported by Rosenkrantz and Zablow (*loc. cit.*) revealed that the alcohol-residue carbon–oxygen linkage for an equatorial acetate yields a single peak at about 1031—1025 cm.$^{-1}$ and that for an axial acetate a single peak at about 1022—1013 cm.$^{-1}$ (see Table 1). The isomeric 2-, 3-, and 4-acetoxy-steroids studied by Fürst *et al.* (*loc. cit.*) appear to show a similar frequency displacement; it is noteworthy that the 4-acetoxycholestanes appear to conform to our generalisation. The

* Part X, *J.*, 1955, 447.

frequency differences are smaller than those reported for 2-, 3-, and 4-hydroxy-steroids, but can be detected in the spectra of CS_2 solutions; Nujol mull and potassium bromide disc spectra are less satisfactory for this purpose.

The frequency of the alcohol-residue carbon–oxygen stretching linkage is affected by the introduction of substituents at the α-carbon atom to the acetate group and by the presence of an enol-acetate system; these frequency displacements may be of value for structure assignments, but they need further investigation.

TABLE 1. *Alcohol-residue carbon–oxygen stretching frequency assignments for 3-acetoxy-steroids in CS_2 solution.*

Compound	Type of steroid	Frequency ($cm.^{-1}$)	Confign. of C–O bond *
Androsterone acetate (3α-acetoxyandrostan-17-one) ...	3α-Acetoxy-5α-	1013 †	a
3α-Acetoxyandrost-16-ene	,,	1020 †	a
3α-Acetoxyandrost-11(?)-en-17-one	,,	1022 †	a
3α-Acetoxy*allo*cholan-17-one	3α-Acetoxy-5β-	1029 †	e
3α : 17β-Diacetoxy*allo*cholan-11-one	,,	1028 †	e
3α : 20α-Diacetoxypregnan-11-one	,,	1027 †	e
3α-Acetoxy-17α-hydroxypregnan-20-one	,,	1026 †	e
Sarsasapogenin acetate	3β-Acetoxy-5β-	1022	a
cyclo-ψ-Sarsasapogenin acetate	,,	1018	a
cyclo-ψ-Smilagenin acetate	,,	1020	a
Ergostanyl acetate (3β-acetoxyergostane)	3β-Acetoxy-5α-	1031 †	e
α-Ergostenyl acetate [3β-acetoxyergost-8(14)-ene]	,,	1028 †	e
γ-Ergostenyl acetate (3β-acetoxyergost-7-ene)	,,	1026 †	e
Tigogenin acetate	,,	1025	e
cyclo-ψ-Tigogenin acetate	,,	1026	e
*neo*Tigogenin acetate	,,	1026	e
cyclo-ψ-*neo*Tigogenin acetate	,,	1025	e
Diosgenin acetate	3β-Acetoxy-5-ene	1030	e
cyclo-ψ-Diosgenin acetate	,,	1030	e

* a = axial; e = equatorial. † From Rosenkrantz and Zablow (*loc. cit.*).

Although methoxy- and *gem*-dimethoxy-steroids are well-known compounds, little information on their infrared absorption has been published (cf. Jones and Herling, *loc. cit.*). The infrared spectrum of a simple ether is characterised by an intensely strong carbon–oxygen stretching band near 1100 $cm.^{-1}$, the exact frequency of which depends on the nature of the substituents on either side of the ether link (see Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 99).

TABLE 2. *Carbon–oxygen stretching frequency assignments for monomethoxy-steroids in CS_2 solution.*

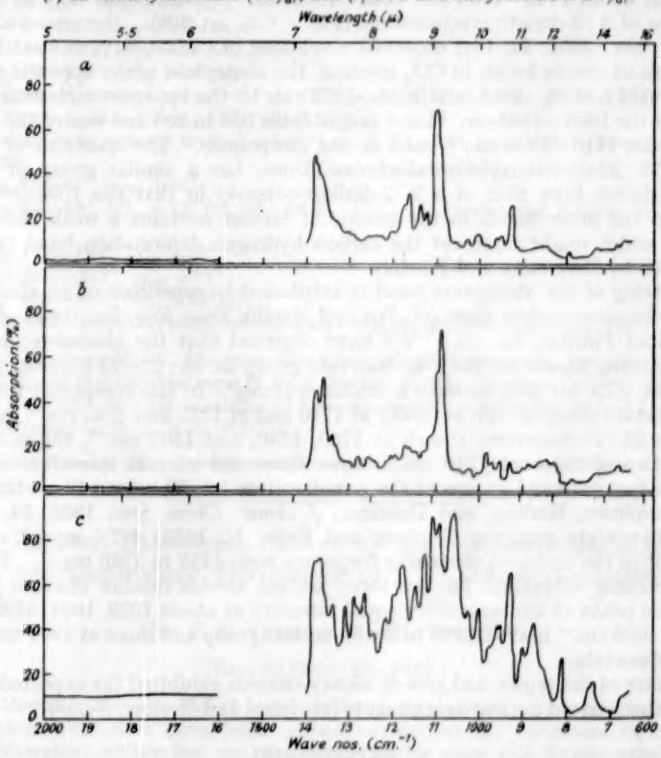
No.	Compound	Type of steroid	Frequency ($cm.^{-1}$)	Confign. of C–O bond
1	3α-Methoxycholestane	3α-Methoxy-5α-	1086	a
2	3α-Methoxycoprostane	3α-Methoxy-5β-	1100	e
3	3β-Methoxycoprostane	3β-Methoxy-5β-	1090	a
4	Sarsasapogenin methyl ether	,,	1088	a
5	3β-Methoxycholestane	3β-Methoxy-5α-	1100	e
6	3β-Methoxy-14-methylcholest-7-en-15-one	,,	1102	e
7	3β-Methoxy-14-methylergosta-7 : 22-diene	,,	1100	e
8	3β-Methoxy-14-methylergosta-7 : 22-dien-15-one	,,	1102	e
9	14-Acetoxy-3β-methoxyergosta-7 : 22-diene	,,	1100	e
10	3β-Methoxycholest-5-ene	3β-Methoxy-5-ene	1104	e
11	6β-Methoxy-3 : 5-*cyclo*ergosta-7 : 9(11) : 22-triene	3 : 5-*cyclo*-6β-Methoxy-	1090	a

A study of the infrared absorption spectra of 3-methoxy-steroids of known stereochemical configuration has shown that in CS_2 solution (see Table 2) an equatorial methoxyl group absorbs strongly between 1100 and 1104 $cm.^{-1}$, and an axial methoxyl between 1086 and 1090 $cm.^{-1}$; the apparent molecular extinction coefficients of the bands range from about 400 to 300. The equatorial methoxyl groups in 3β-methoxycholestane (Fig. *a*, C.S. no. 204 *) and 3α-methoxycoprostane (C.S. no. 205) absorb at about 1100, and the

* Spectra thus designated have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained, on application quoting the C.S. no., from the General Secretary, the Chemical Society, Burlington House, Piccadilly, London, W.1.

axial groups in 3α-methoxycholestane (Fig. *b*, C.S. no. 206) and 3β-methoxycoprostane (C.S. no. 207) at about 1088 cm.$^{-1}$. These characteristic absorption frequencies are unaffected by other steroid nuclear substituents, such as double bonds at positions 5, 7, and 22 (cf. cholesteryl methyl ether and 3β-methoxy-14-methylergosta-7 : 22-diene) or a spirostan side-chain (cf. sarsasapogenin methyl ether). The spectra of the 3-methoxysteroids contained a band of medium intensity at about 1175 cm.$^{-1}$, which might also be associated with the ether linkage.

Infrared spectra of solutions in carbon disulphide of (*a*) *3β-methoxycholestane* (1·0%), (*b*) *3α-methoxycholestane* (1·0%), *and* (*c*) *3 : 3-dimethoxycholestane* 2·0%).



Josien, Fuson, and Carey (*J. Amer. Chem. Soc.*, 1951, **73**, 4445) reported that 3β-methoxy-5-ene-steroids in CS_2 solution absorb at about 1103 cm.$^{-1}$ and 6-methoxy-3 : 5-*cyclo*-steroids at about 1098 cm.$^{-1}$; they suggested that the difference in carbon–oxygen stretching frequency could be used to distinguish between 3β-methoxy-5-ene- and 6β-methoxy-3 : 5-*cyclo*-steroids. We believe that the frequency displacement (cf. "*i*-dehydroergosteryl methyl ether") is probably caused by the different configuration of the methoxyl groups rather than by the double-bond character of the 3 : 5-*cyclo*-group; the 3β-methoxyl group is equatorial and would be expected to absorb at a slightly higher frequency than the 6β-methoxyl, which is axial. Corey *et al.* (*loc. cit.*) observed similar displacements of the carbon–deuterium stretching bands for 6β-deutero-5α- and 6β-deutero-3 : 5-*cyclo*-steroids compared with those for 3β-deutero-5α- and 3β-deutero-5-ene-steroids.

The carbon–oxygen stretching bands for a 3 : 3-dialkoxy-steroid (see Table 3) do not appear, as might have been expected, at about 1102 and 1090 cm.$^{-1}$, but instead split into four components that absorb at about 1190—1175, 1155—1132, 1110—1100, and 1053—1050 cm.$^{-1}$, the absorption bands at 1190—1175 and 1155—1132 cm.$^{-1}$ being weaker

TABLE 3. *Carbon–oxygen stretching frequency assignments for* gem*-dialkoxy-steroids in* CS_2 *solution.*

No.	Compound	Frequency ($cm.^{-1}$)
12	3 : 3-Dimethoxycholestane	1175, 1136, 1107, 1050
13	3 : 3-Diethoxycholestane	1183, 1132, 1110, 1053
14*	17α : 21-Dihydroxy-3 : 3-dimethoxy*allo*pregnane-11 : 20-dione	1182, 1155, 1101, 1050
15*	21-Acetoxy-17α-hydroxy-3 : 3-dimethoxy*allo*pregnane-11 : 20-dione	1190, 1135, 1100, 1052
16	3β-Acetoxy-22 : 22-dimethoxybisnor*allo*cholan-11-one	1185, 1143, 1095, 1064

* As Nujol mull.

than those at about 1110—1100 and 1053—1050 $cm.^{-1}$; these bands may be observed in the spectrum of 3 : 3-dimethoxycholestane (Fig. *c*, C.S. no. 268). Bergmann and Pinchas (*Rec. Trav. chim.*, 1952, **71**, 161) observed a splitting of carbon–oxygen stretching bands in the spectra of simple ketals in CCl_4 solution, the absorption peaks appearing at 1190—1158, 1143—1124, 1098—1063, and 1056—1038 $cm.^{-1}$; the apparent molecular extinction coefficient of the 1098—1063-$cm.^{-1}$ band ranged from 500 to 200 and was of the same order as that for the 1110—1100-$cm.^{-1}$ band in our compounds. The spectrum of the acetal, 3β-acetoxy-22 : 22-dimethoxybisnor*allo*cholan-11-one, has a similar group of absorption bands, but differs from that of a 3 : 3-dialkoxy-steroid in that the 1095-$cm.^{-1}$ band is weaker than the other bands in the group; it further contains a weak band at about 1108 $cm.^{-1}$, which might represent the carbon–hydrogen deformation band reported for simple acetals by Bergmann and Pinchas.

The splitting of the absorption band is attributed to repetition of an absorbing substituent on the same carbon atom (cf. Fox and Martin, *Proc. Roy. Soc.*, 1938, *A*, **167**, 257; Bergmann and Pinchas, *loc. cit.*). We have observed that the alcohol-residue carbon–oxygen stretching bands for the *gem*-diacetate group in 3β : 22 : 22-triacetoxybisnor*allo*cholan-11-one (C.S. no. 209) undergo a similar splitting. In this compound the 11-ketone and the 3-acetate group absorb normally at 1710 and at 1732 and 1240 $cm.^{-1}$, respectively, whereas the 22 : 22-diacetates absorb at 1760, 1240, and 1202 $cm.^{-1}$, the peaks at 1760 having twice and those at 1240 $cm.^{-1}$ three times the normal intensity. Interaction between the two carbonyl groups of the *gem*-diacetate [cf. 20-ketone 21-acetate grouping (Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820) and 11-ketone 12-acetate grouping (Dickson and Page, *J.*, 1955, 447)] would account for displacement of the carbonyl stretching frequency from 1735 to 1760 $cm.^{-1}$. The carbon–oxygen stretching vibrations for the three acetate alcohol-residue linkages yield three characteristic peaks of approximately equal intensity at about 1026, 1004, and 972 $cm.^{-1}$; the peak at 1026 $cm.^{-1}$ is attributed to the 3β-acetate group and those at 1004 and 972 $cm.^{-1}$ to the *gem*-diacetate.

The spectra of the mono- and *gem*-di-alkoxy-steroids exhibited the expected absorption bands for other steroid nuclear substituents (cf. Jones and Herling, *loc. cit.*)

EXPERIMENTAL

The spectroscopic measurements were made with a Perkin-Elmer Corporation, model 21, double-beam, infrared spectrophotometer fitted with a sodium chloride prism (see Dickson, Page, and Rogers, *J.*, 1955, 443). Compounds sufficiently soluble in carbon disulphide and carbon tetrachloride were examined as 1·0% (w/v) solutions in 1·0-mm. sodium chloride cells. Compounds that were insoluble in carbon disulphide were examined as Nujol mulls. Bromoform and chloroform are unsuitable solvents for studying 3 : 3-dimethoxy-steroids; bromoform absorbs in the 1100-$cm.^{-1}$ region, and chloroform, which transmits between 1200 and 1000 $cm.^{-1}$ absorbs between 1270 and 1200 $cm.^{-1}$.

The steroidal sapogenins and derivatives listed in Table 1 have been described by Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page (*J.*, 1955, 1966). The monomethoxy-steroids, which had been provided by Professor D. H. R. Barton, F.R.S., and Professor C. W. Shoppee, and the dialkoxy- and 22 : 22-diacetoxy-steroids, which had been prepared in these laboratories (see previous and subsequent papers in the present series), had the properties given below, references below being (*a*) Lewis and Shoppee (*J.*, 1955, 1365, 1375,), (*b*) Nace (*J. Amer. Chem. Soc.*, 1952, **74**, 5937), (*c*) Babcock and Fieser (*ibid.*, p. 5472), (*d*) Barton, Ives, Kelly, Woodward, and Patchett (*J.*, in the press), (*e*) *idem* (*Chem. and Ind.*, 1954, 605), (*f*) Cameron,

Hunt, Oughton, Wilkinson, and Wilson (*J.*, 1953, 3864) (for names of compounds see Tables 2 and 3):

(1) m. p. 63°, $[\alpha]_D$ +21° (*a*) {cf. m. p. 63°, $[\alpha]_D$ +18° (*b*)}.
(2) m. p. 88°, $[\alpha]_D$ +32° [prepared by methylation of coprostan-3α-ol (*a*)].
(3) m. p. 78°, $[\alpha]_D$ +28° (*a*) {cf. m. p. 63°, $[\alpha]_D$ +27° (*c*), double m. p. 64° and 79°, $[\alpha]_D$ +23° (Evans and Shoppee, *J.*, 1953, 540)}.
(4) (prepared by methylation of sarsasapogenin and hence probably 3β-methoxy-5β : 22*b*-spirostan), m. p. 155—158° [cf. 153—155° (Farmer and Kon, *J.*, 1937, 414)].
(5) m. p. 83°, $[\alpha]_D$ +20° (*a*) {cf. m. p. 82°, $[\alpha]_D$ +21° (*c*), m. p. 81—82°, $[\alpha]_D$ +20° (*b*)}.
(6) m. p. 86—87°, $[\alpha]_D$ +56° (*d*).
(7) m. p. 99—100°, $[\alpha]_D$ −24° (*e*).
(8) m. p. 124—126°, $[\alpha]_D$ +31° (*e*).
(9) m. p. 129—130°, $[\alpha]_D$ +14° (*d*).
(10) (cholesteryl methyl ether) m. p. 82°, $[\alpha]_D$ −41·5° {cf. m. p. 84·5—85°, $[\alpha]_D$ −46° (Müller and Page, *J. Biol. Chem.*, 1933, **101**, 127)}.
(11) ("*i*-dehydroergosteryl methyl ether") m. p. 53—54°, $[\alpha]_D$ +137° (Rees and Shoppee, *J.*, 1954, 3422).
(12) m. p. 81—82°, $[\alpha]_D$ +24°.
(13) m. p. 65—68°, $[\alpha]_D$ +22° {cf. 68—69·5°, $[\alpha]_D$ +26° (Serini and Köster, *Ber.*, 1938, **71**, 1766)}.
(14) m. p. 177—181°, $[\alpha]_D$ +52°.
(15) m. p. 205—212°, $[\alpha]_D$ +87°.
(16) m. p. 183—185°, $[\alpha]_D$ +28° (*f*).
(17) 3β : 22 : 22-Triacetoxybisnor*allo*cholan-11-one, m. p. 160—162°, $[\alpha]_D$ +9° (*f*).

We thank Professor C. W. Shoppee (University College, Swansea) for specimens of (1), (2), (3), (5), (10), and (11) and Professor D. H. R. Barton, F.R.S. (Birkbeck College), for specimens of (4), (6), (7), (8), and (9); the specimen of sarsasapogenin methyl ether (4) had been prepared by the late Professor G. A. R. Kon, F.R.S.

GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX. [*Received, February 15th*, 1955.]

Potential Tumour Inhibitors. Esters of 4-Di-(2-hydroxyethyl)aminopyridine and Quaternary Derivatives of 2 : 3-Dihydroglyoxalino[1 : 2-a]pyridine.

By F. C. COPP and G. M. TIMMIS.

[Reprint Order No. 6153.]

Reaction between 4-di-(2-hydroxyethyl)aminopyridine and a number of sulphonyl chlorides gave (with certain exceptions) the corresponding di-sulphonyloxy-amines but use of thionyl chloride gave 4-di-(2-chloroethyl)-aminopyridine. Unlike the corresponding benzene derivative, the sulphonic esters were basic and formed stable salts and methiodides. Similar attempts to esterify 2-di-(2-hydroxyethyl)aminopyridine and 2-di-(2-hydroxyethyl)-amino-5-nitropyridine gave 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridinium salts (or isomers). Methylation of 2 : 3-dihydro- and 2 : 3-dihydro-6-nitro-glyoxalino[1 : 2-*a*]pyridine takes place in the 1-position, but 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine and ethylene dibromide gave a mixture.

SOME members of a series of sulphonic esters, originally prepared in these laboratories and derived from *NN*-di-(2-hydroxyethyl)aniline; *e.g.*, *NN*-di-(2-toluene-*p*-sulphonyloxyethyl)-aniline and its *p*-chloro-analogue (I; R = H or Cl respectively) (B.P. 662,645) markedly inhibited the growth of the Walker tumour in rats (Ann. Reports, British Empire Cancer Campaign, 1949, p. 43; Haddow and Timmis, Acta Union Intern. contre le Cancre, 1951, Vol. VII, p. 469). The activity of these esters, which, as alkylating agents, are related to the active aryl nitrogen mustards (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 82; Ross, *J.*, 1949, 183 *et seq.*), suggested the preparation of related heterocyclic compounds.

4-Di-(2-hydroxyethyl)aminopyridine (II; R = OH), prepared from 4-chloropyridine and excess of diethanolamine at 180°, reacted smoothly in pyridine with methanesulphonyl chloride and with aromatic sulphonyl chlorides except those carrying an electron-attracting group. The expected esters (II; R = O·SO_2·C_7H_7) separated initially as salts (see Table) which gave the parent bases on treatment with excess of ammonia. These bases were readily converted into methiodides to which the structure (III) has been tentatively assigned (cf. Tschitschibabin and Konowalowa, *Ber.*, 1926, **59**, 2055; Mann and Watson, *J. Org. Chem.*, 1948, **13**, 507). With thionyl chloride, the alcohol gave the hydrochloride of the dichloride (II; R = Cl) which also afforded a crystalline base and methiodide. These pyridine esters were evidently more powerful bases than the corresponding arylamine compounds; *e.g.*, the sulphonates (I; R = H or Cl) were found by one of us (G. M. T.) to be feebly basic, resembling the analogous chloroethyl compounds (Ross, *J.*, 1949, 183). An appreciable difference is also found between the basic strengths of the corresponding primary amines [cf. 4-aminopyridine, pK_a 9·2 (Albert, *J.*, 1951, 1376); aniline, pK_a

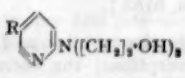
(I)

(II)

(III)

4·65 (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469)]. Some of the salts of the pyridine sulphonate esters were electrometrically titrated by Dr. T. S. G. Jones; in 50% aqueous acetone they had pK_a' between 7·2 and 7·4 (see Table).

As was expected from Bremer's work (*Annalen*, 1936, **521**, 286) similar attempts to prepare analogous esters from 2-di-(2-hydroxyethyl)aminopyridine (IV; R = H) and 2-di-(2-hydroxyethyl)amino-5-nitropyridine (IV; R = NO_2) led to 2 : 3-dihydroglyoxalino-[1 : 2-*a*]pyridinium salts (V) (Ring Index, No. 765) (an alternative formulation is discussed below). *E.g.*, equimolar proportions of (IV; R = NO_2) and 4-methyl-3-nitrobenzenesulphonyl chloride gave 2 : 3-dihydro-1-2′-hydroxyethyl-6-nitroglyoxalino[1 : 2-*a*]pyridinium chloride (V; R = NO_2, R′ = OH, X = Cl), whilst two mols. of the acid chloride afforded 2 : 3-dihydro-1-(2-4′-methyl-3′-nitrobenzenesulphonyloxyethyl)-6-nitroglyoxalino[1 : 2-*a*]pyridinium 4-methyl-3-nitrobenzenesulphonate (V; R = NO_2, R′ = X = 3 : 4 : 1-NO_2·C_6H_3Me·SO_3). The isolation of these salts was, of course, complicated by the different possible combinations of cations and anions in the crude reaction mixture. Three analogous salts (V; R = NO_2, R′ = *p*-NHAc·C_6H_4·SO_3, X = Cl; R = H, R′ = OH, X = 3 : 4 : 1-NO_2·C_6H_3Me·SO_3; and R = H, R′ = X = *p*-NHAc·C_6H_4·SO_3) were similarly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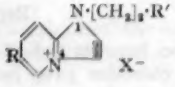
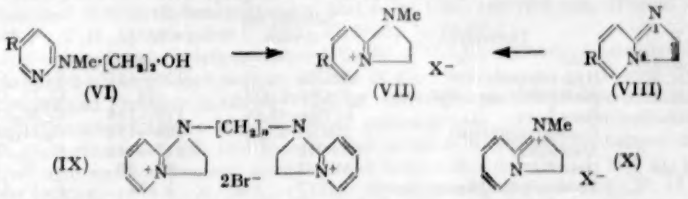

(V)

prepared. With thionyl chloride, the alcohol (IV; R = NO_2) gave the chloride (VII; R = NO_2, R′ = X = Cl). All the analyses of these compounds were complicated by hydration.

Since the salt (V; R = NO_2, R′ = OH, X = Cl) slightly (but temporarily) inhibited the growth of the Walker tumour in rats, some exploratory work was carried out on an alternative synthesis. Raison's work (*J.*, 1939, 3319) suggested that quaternisation of the parent 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridines (VIII) should take place on the doubly bound nitrogen of the amidine system which is present, *i.e.*, at position 1, and Osbond (*J.*, 1950, 1853) reached similar conclusions for the related 2 : 3-dihydroglyoxalino[1 : 2-*a*]-quinolines. This was confirmed in two simple instances. 2-(*N*-2-Hydroxyethyl-*N*-methylamino)pyridine (VI; R = H) was prepared from 2-bromopyridine and 2-*N*-methylaminoethanol; it was converted by thionyl chloride (cf. Bremer, *loc. cit.*) into the chloride (VII; R = H, X = Cl) and thence into (VII; R = H, X = I) which was identical with the product obtained from 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine (VIII; R = H) (see below) and methyl iodide. Similarly the synthesis of the nitro-iodide (VII; R = NO_2, X = I) by these two procedures also gave indistinguishable products. The base (VIII; R = H)

has been previously synthesised (*idem*, *loc. cit.*) and its m. p. reported to be 64—65°, whereas we found m. p. 37—39°. It seems likely that the former product was a monohydrate since on exposure to water vapour our product, m. p. 37—39°, was converted into a monohydrate, m. p. 60—61°. It is noteworthy that Bremer dried his material before analysis which would account for his correct analytical figure; in agreement with this author, the picrate had m. p. 213°.

The base (VIII; R = H) and ethylene dibromide gave a mixture of two substances which, in accordance with the above conclusions, have been assigned structures (V; R = H, R′ = X = Br) (or its isomer, see below) and (IX; $n = 2$). The same mixture resulted



when ethylene dibromide was used in large excess; it seems likely that in the monosalt first formed (V) the powerful electron-attracting effect of the quaternary grouping—possibly relayed through the amidine group (see below)—makes the bromine atom in the side chain more susceptible than the bromine atoms in ethylene dibromide to nucleophilic attack by the base (VIII; R = H). The salt (IX; $n = 3$) was similarly prepared.

In the above quaternary compounds it seems likely that the preferred location of the quaternary centre is position 4, as in (VII), since such a formulation permits free resonance in the pyridine ring. However, as far as we are aware there is no direct evidence which completely excludes the alternative formulation (X), and this reservation applies to all structures which we have based above on (V), (VII), and (IX). The interchangeability of the two quaternary centres is implicit in the alternative syntheses described above.

The results of tests for tumour-inhibitory activity were disappointing. Of the compounds tested by Prof. A. Haddow on the Walker 256 carcino-sarcoma in the rat, according to the method described by Badger, Elson, Haddow, Hewett, and Robinson (*Proc. Roy. Soc.*, 1942, *B*, **130**, 255), only (II; R = O·SO_2·C_6H_4·NHAc-*p*) induced a definite (but slight) inhibition of growth of the tumour.

Experimental

4-Di-(2-hydroxyethyl)aminopyridine (II).—4-Chloropyridine (8·9 g.) (Wibaut and Brockman, *Rec. Trav. chim.*, 1939, **58**, 885) and diethanolamine (30 g.) were heated together at ~180° for 5 hr., then poured into a suspension of powdered anhydrous sodium carbonate (12 g.) in propan-2-ol (150 ml.) and refluxed therein for 30 min. After being kept overnight at 0° the insoluble inorganic solids were filtered off, the filtrate was evaporated, and the residue distilled *in vacuo*. *4-Di-(2-hydroxyethyl)aminopyridine* resulted as a viscous liquid, b. p. 220—225°/0·05 mm. (7·8 g.), which rapidly crystallised. It was insoluble in chloroform, ethyl acetate, and acetone and recrystallised from propan-2-ol and acetone as slender pointed prisms, m. p. 108·5—110° (Found: C, 59·5; H, 7·75. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7%).

Reaction of 4-Di-(2-hydroxyethyl)aminopyridine with Sulphonyl Chlorides.—A suspension of 4-di-(2-hydroxyethyl)aminopyridine (3·6 g.; 0·02 mol.) in dry pyridine (15 ml.) was stirred at *ca.* 5° during the gradual addition of the sulphonyl chloride (0·05 mol.). The mixture was kept at 5° for a further 15 min. and then allowed to warm spontaneously to a maximum temperature of 30°. After 1 hr. the mixture was poured into cold water, giving the products as solids, or as oils which subsequently solidified. These were filtered off, washed, and dried thoroughly *in vacuo* before recrystallisation (see Table). At this stage the products were obtained as the salts described in the Table. The solid parent bases were regenerated by grinding these salts with excess of 2N-ammonia and filtration. The methiodides were prepared in anhydrous methanol. The product from methanesulphonyl chloride was water-soluble and was therefore isolated by precipitation with propan-2-ol; the liquid base was isolated by extraction with ethyl acetate since it was immiscible with ether. *p*-Chlorobenzenesulphonyl chloride and

4-methyl-3-nitrobenzenesulphonyl chloride gave no identifiable products in the above reaction although different conditions and isolation procedures were investigated.

4-Di-(2-sulphanilyloxyethyl)pyridine.—4-Di-(2-*N*-acetylsulphanilyloxyethyl)pyridine (3·6 g.) dissolved in methanol (60 ml.) when a rapid stream of hydrogen chloride was passed in. The product crystallised; the mixture was then cooled and the solid 4-di-(2-sulphanilyloxyethyl)-pyridine trihydrochloride was filtered off. It recrystallised from a large volume of methanol containing a little hydrogen chloride. The free base, prepared by means of aqueous sodium carbonate, was dried *in vacuo* (2·2 g.). Its recrystallisation caused considerable loss.

Esters (II; R = $O{\cdot}SO_2R'$).

No.	R	Derivative	Solvent for crystn.	M. p.	Formula
1	Me	Base	—	Liquid	—
2	,, ...	*Hydrochloride*	EtOH	120—121°	$C_{11}H_{19}O_6N_2ClS_2$
3	,, ...	*Methiodide monohydrate*	EtOH–EtOAc	74	$C_{12}H_{21}O_6N_2IS_2,H_2O$
4	Ph	*Base* *	$COMe_2$–H_2O	115—116	$C_{21}H_{22}O_6N_2S_2$
5	,, ...	*Benzenesulphonate*	MeOH–Et_2O	133—134	$C_{27}H_{26}O_9N_2S_3$
6	,, ...	*Methiodide*	EtOH	117—118	$C_{22}H_{25}O_6N_2IS_2$
7	*p*-C_6H_4Me ...	*Base* *	MeOH	82—86	$C_{23}H_{26}O_6N_2S_2$
8	,, ...	*Toluene*-p-*sulphonate monohydrate* *	EtOH	152	$C_{30}H_{34}O_9N_2S_3,H_2O$
9	,, ...	*Methiodide* *	MeOH	95—96	$C_{24}H_{29}O_6N_2IS_2$
10	*p*-MeO·C_6H_4	*Base*	MeOH	95—96	$C_{23}H_{26}O_8N_2S_2$
11	,,	p-*Methoxybenzenesulphonate*	MeOH	96—98	$C_{30}H_{34}O_{12}N_2S_3$
12	*p*-NHAc·C_6H_4	*Base*	EtOH	200—201	$C_{25}H_{28}O_8N_4S_2$
13	,,	*Hydrochloride*	EtOH	150—152	$C_{25}H_{29}O_8N_4ClS_2$
14	,,	*Methiodide*	H_2O	168—169	$C_{26}H_{31}O_8N_4IS_2$
15	*p*-$NH_2{\cdot}C_6H_4$	*Base*	EtOH	Collapse 170; decomp. >260	$C_{21}H_{24}O_6N_4S_2$
16	,,	*Trihydrochloride*	MeOH	Soft, 166; decomp. >220	$C_{21}H_{27}O_6N_4Cl_3S_2$
17	2-$C_{10}H_7$	*Base*	$COMe_2$–H_2O	155—158; soft, 130	$C_{29}H_{28}O_6N_2S_2$
18	,, ...	Naphthalene-2-sulphonate †	$MeNO_2$	203	$C_{29}H_{24}O_9N_2S_3$

No.	Found (%) C	H	N		Required (%) C	H	N		pK_a'
1	—	—	—	—	—	—	—	—	7·4
2	35·4	5·05	7·3	—	35·3	5·1	7·5	—	—
3	29·0	4·7	—	I, 25·7	28·9	4·7	—	I, 25·5	—
4	54·55	4·9	6·1	S, 13·8	54·5	4·8	6·1	S, 13·8	7·2
5	52·4	4·5	—	—	52·3	4·55	—	—	—
6	—	—	—	I, 21·1	—	—	—	I, 21·0	—
7	55·8	5·15	—	—	56·3	5·3	—	—	7·4
8	53·1	5·4	3·8	S, 14·1	52·9	5·3	4·1	S, 14·1	—
9	—	—	—	I, 20·1	—	—	—	I, 20·1	—
10	52·6	5·2	—	—	52·9	5·0	—	—	7·4
11	50·6	4·95	3·6	S, 13·2	50·7	4·8	3·9	S, 13·5	—
12	51·9	5·1	9·9	—	52·1	4·9	9·7	—	7·4
13	49·2	4·7	8·9	—	49·0	4·8	9·1	—	—
14	43·6	4·7	7·6	—	43·5	4·35	7·8	—	—
15	51·3	4·9	—	—	51·2	4·9	—	—	—
16	—	—	9·5	S, 10·1	—	—	9·3	S, 10·6	—
17	61·6	4·6	—	—	62·0	4·6	—	—	7·4
18	60·65	4·4	—	S, 12·3	60·8	4·4	—	S, 12·4	—

* Unstable on repeated crystallisation or prolonged storage.

† Required 48 hours' treatment with conc. ammonia to liberate the free base.

4-Di-(2-chloroethyl)aminopyridine.—Thionyl chloride (2 g.) was slowly added to a cooled suspension of 4-di-(2-hydroxyethyl)aminopyridine (1 g.) in chloroform (5 ml.), and the mixture heated under reflux for 2 hr. Addition of ether gave *4-di-(2-chloroethyl)aminopyridine hydrochloride* as a gum which crystallised from propan-2-ol in short flat prisms (1·3 g.), m. p. 172—173° (Found: C, 42·5; H, 5·1; Cl, 41·7. $C_9H_{13}N_2Cl_3$ requires C, 42·3; H, 5·1; Cl, 41·6%). With cold aqueous potassium carbonate this hydrochloride gave the *base* which, crystallised by dissolution in cold benzene and slow addition of light petroleum (b. p. 40—60°), had m. p. 131—132·5° (Found: C, 49·4; H, 5·5; Cl, 32·3. $C_9H_{12}N_2Cl_2$ requires C, 49·35; H, 5·5; Cl, 32·3%). The *methiodide*, prepared in acetone at room temperature and crystallised from ethanol, had

m. p. 204° (decomp.) (Found : C, 33·2; H, 4·2; N, 7·7. $C_{10}H_{12}N_2Cl_2I$ requires C, 33·3; H, 4·2; N, 7·8%).

2-Di-(2-hydroxyethyl)aminopyridine (IV; R = H).—This was prepared from 2-bromopyridine (15·8 g.) and diethanolamine (31 g.) according to Weiner and Kaye's method (*J. Org. Chem.*, 1949, **14**, 868) except that the free bases were liberated with sodium carbonate (20 g.) in propan-2-ol (200 ml.) as above. The inorganic salts were filtered off, the filtrate was evaporated, and the residue distilled *in vacuo*, giving 2-di-(2-hydroxyethyl)aminopyridine, b. p. 158—165°/0·01 mm. (10·5 g.) (Found : N, 15·7. Calc. for $C_9H_{14}O_2N_2$: N, 15·4%). Distillation gave a tarry residue, particularly from larger batches.

2-(N-2-Hydroxyethyl-N-methylamino)pyridine (VI; R = H), similarly prepared from 2-bromopyridine and 2-*N*-methylaminoethanol, had b. p. 106—108°/0·9 mm. (Found : C, 62·9; H, 7·7; N, 18·5. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·95; N, 18·4%).

2-Di-(2-hydroxyethyl)amino-5-nitropyridine (IV; R = NO_2).—2-Chloro-5-nitropyridine (4 g.), diethanolamine (3·5 g.) and fused sodium acetate (2·1 g.) were heated in ethanol (20 ml.) for 3 hr. (cf. Mangini and Frengalli, *Gazzetta*, 1939, **69**, 86). The resulting suspension was filtered whilst hot and the cooled filtrate rapidly deposited golden prisms. These were collected, washed with a little fresh ethanol, dried, and then heated *in vacuo* to remove unchanged 2-chloro-5-nitropyridine. The residual *product*, recrystallised from water or ethanol, had m. p. 103·5—105° (Found : C, 47·6; H, 5·5; N, 18·7. $C_9H_{13}O_4N_3$ requires C, 47·6; H, 5·8; N, 18·5%).

2-(N-2-Hydroxyethyl-N-methylamino)-5-nitropyridine (VI; R = NO_2), similarly prepared, crystallised from methanol in bright yellow needles, m. p. 86·5—87·5° (Found : C, 48·5; H, 5·5; N, 21·2. $C_8H_{11}O_3N_3$ requires C, 48·7; H, 5·6; N, 21·3%).

Reaction of 2-Di-(2-hydroxyethyl)amino-5-nitropyridine and 4-Methyl-3-nitrobenzenesulphonyl chloride.—(*a*) A suspension of 2-di-(2-hydroxyethyl)amino-5-nitropyridine (2·3 g.; 0·01 mol.) in dry pyridine (4 ml.) was stirred at 5—10° whilst 4-methyl-3-nitrobenzenesulphonyl chloride (2·5 g.; 0·01 mol.) was added during 30 min. The mixture was kept at 5—10° for a further 30 min., then allowed to warm spontaneously. After 4 hr. the resulting suspension was stirred into dry acetone, a yellow precipitate separating. This was filtered off and crystallised twice from ethanol giving very pale yellow needles (1·5 g.) of *2 : 3-dihydro-1-2′-hydroxyethyl-6-nitroglyoxalino*[1 : 2-*a*]*pyridinium chloride*, m. p. 204—205° (V; R = NO_2, R′ = OH, X = Cl) (Found : C, 44·3; H, 4·9; N, 17·7; Cl, 13·8. $C_9H_{12}O_5N_3Cl$ requires C, 44·0; H, 4·9; N, 17·1; Cl, 14·4%), which gradually decomposed.

(*b*) Use of twice as much 4-methyl-3-nitrobenzenesulphonyl chloride in dry pyridine (8 ml.) at 5—10° gave *2 : 3-dihydro-1-(2-4′-methyl-3′-nitrobenzenesulphonyloxyethyl)-6-nitroglyoxalino*[1 : 2-*a*]*pyridinium 4-methyl-3-nitrobenzenesulphonate monohydrate* (2·1 g.), m. p. 152—154° (from methanol–ether) (Found : C, 43·1; H, 3·8; N, 10·8; loss on drying, 2·0. $C_{23}H_{23}O_{12}N_5S_2,H_2O$ requires C, 42·9; H, 3·9; N, 10·9; H_2O, 2·8%).

1-(2-N-Acetylsulphanilyloxyethyl)-2 : 3-dihydro-6-nitroglyoxalino[1 : 2-*a*]*pyridinium chloride dihydrate*, similarly prepared from equimolecular amounts of 2-di-(2-hydroxyethyl)-5-nitropyridine and *N*-acetylsulphanilyl chloride, crystallised from ethanol containing 5% of water, as prisms, m. p. 129—130° (Found : C, 43·0; H, 4·6; N, 11·4; Cl, 7·4; S, 6·5. $C_{17}H_{19}O_6N_4ClS,2H_2O$ requires C, 42·65; H, 4·8; N, 11·7; Cl, 7·4; S, 6·7%).

2-Di-(2-hydroxyethyl)aminopyridine and Sulphonyl Chlorides.—Under similar conditions 2-di-(2-hydroxyethyl)aminopyridine and one equivalent of 4-methyl-3-nitrobenzenesulphonyl chloride gave *2 : 3-dihydro-1-2′-hydroxyethylglyoxalino*[1 : 2-*a*]*pyridinium 4-methyl-3-nitrobenzenesulphonate*, which crystallised from propan-2-ol as prisms, m. p. 126·5—127·5° (Found : C, 50·55; H, 5·0; N, 11·3; S, 8·3. $C_{16}H_{19}O_6N_3S$ requires C, 50·4; H, 5·0; N, 11·0; S, 8·4%). With two equivalents of *N*-acetylsulphanilyl chloride there resulted *1-(2-N-acetylsuphanilyloxyethyl)-2 : 3-dihydroglyoxalino*[1 : 2-*a*]*pyridinium N-acetylsulphanilate monohydrate*, m. p. 178—180° (from propan-2-ol) (Found : C, 50·2; H, 5·0. $C_{31}H_{33}O_8N_4S_2,H_2O$ requires C, 50·5; H, 5·0%).

1-2′-Chloroethyl-2 : 3-dihydro-6-nitroglyoxalino[1 : 2-*a*]*pyridinium Chloride* (V; R = NO_2, R′ = X = Cl).—2-Di-(2-hydroxyethyl)amino-5-nitropyridine (12 g.) was suspended in chloroform (30 ml.) and cooled to 10—15° during the gradual addition of thionyl chloride (16 g.). After 1 hr. at room temperature the mixture was heated to reflux for 3 hr., then cooled and the insoluble solid was filtered off and dried immediately *in vacuo* to remove occluded acid. It was then dissolved in hot propan-2-ol, and pyridine was added until the solution was no longer strongly acid. Ether was then slowly added to turbidity and, on cooling, needles rapidly separated. [Without the neutralisation the product could not be obtained free from acid though analysis indicated that it was substantially (V; R = NO_2, R′ = X = Cl) and not

2-di-(2-chloroethyl)-5-nitropyridine hydrochloride.] This product (V; R = NO_2, R′ = X = Cl) crystallised from propan-2-ol in needles, apparently the *monohydrate*, m. p. 82—84° (Found: C, 38·5; H, 4·6; O, 16·3; N, 15·1; Cl, 26·0; Cl^-, 13·0; loss at 100°, 5·9. $C_9H_{11}O_2N_3Cl_2,H_2O$ requires C, 38·3; H, 4·6; O, 17·0; N, 14·9; Cl, 25·2; Cl^-, 12·6; H_2O, 6·4%). The dried *salt* was also analysed (Found: C, 41·0; H, 4·2. $C_9H_{11}O_2N_3Cl_2$ requires C, 40·9; H, 4·2%).

2 : 3-*Dihydroxyglyoxalino*[1 : 2-*a*]*pyridine*.—The hydrochloride of the base was prepared by Bremer's method (*loc. cit.*) by gently warming 2-2′-chloroethylaminopyridine or, alternatively, by boiling a benzene solution of this substance for 3 hr., the desired hydrochloride slowly separating. The free base was precipitated from cooled aqueous solution by excess of potassium hydroxide and, crystallised from benzene, had m. p. 60—61°. It rapidly sublimed at 60°/0·1 mm. to give deep yellow needles, m. p. 36—38° (not clear until 48°), of anhydrous 2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridine*. It was analysed immediately (Found: C, 69·2; H, 6·5. $C_7H_8N_2$ requires C, 69·7; H, 6·7%). After 24 hours' exposure, in a sealed vessel, to water vapour the colour had become lighter and, after drainage on a porous tile, the m. p. was 60—61° (Found: C, 60·85; H, 7·3; N, 20·0; O, 10·9. $C_7H_8N_2,H_2O$ requires C, 60·85; H, 7·3; N, 20·3; O, 11·6%). Its *picrate* formed golden needles, m. p. 213° (Found: C, 44·7; H, 3·0. $C_{13}H_{11}O_7N_5$ requires C, 44·7; H, 3·2%). Bremer (*loc. cit.*) also found m. p. 213° but gave no analysis.

2 : 3-Dihydro-6-nitroglyoxalino[1 : 2-*a*]pyridine was obtained by the method previously recorded (*idem, loc. cit.*); it decomposed at 258—259°.

2 : 3-*Dihydro*-1-*methylglyoxalino*[1 : 2-*a*]*pyridinium Iodide* (VII; R = H; X = I).—To 2-(*N*-2-hydroxyethyl-*N*-methylamino)pyridine (10 g.) in chloroform (30 ml.) thionyl chloride (10 ml.) was slowly added with cooling. The mixture was then refluxed for 1 hr. and the chloroform removed *in vacuo*. The residue was dissolved in cold water (20 ml.), the solution made alkaline with excess of potassium carbonate, and the precipitated oil extracted with ether. The ethereal solution was rapidly dried and evaporated and the residue warmed on the steam-bath until it crystallised. This solid was added to a suspension of powdered potassium iodide (10 g.) in boiling ethanol (30 ml.), a precipitate of potassium chloride being rapidly formed. This was filtered off and ethyl acetate added to the filtrate to precipitate 2 : 3-*dihydro*-1-*methylglyoxalino*[1 : 2-*a*]*pyridinium iodide* (5·1 g.). This was repeatedly crystallised from propan-2-ol–acetone and finally from ethanol, forming yellowish needles, m. p. 169—170° (Found: I, 48·8. $C_8H_{11}N_2I$ requires N, 10·7; I, 48·4%).

Alternatively, anhydrous 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine (1 g.) and methyl iodide (2 ml.) in methanol (5 ml.) were heated under reflux. After 30 min., the product was precipitated with ethyl acetate and recrystallised from ethanol in cream-coloured needles (2·2 g.), m. p. and mixed m. p. 169—170° (Found: N, 10·7; I, 49·0%).

2 : 3-*Dihydro*-1-*methyl*-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium Iodide*.—2-(*N*-2-Hydroxyethyl-*N*-methylamino)-5-nitropyridine was similarly converted into this *iodide*, yellow prisms, m. p. 246—247° (from methanol) (Found: I, 41·4. $C_8H_{10}O_2N_3I$ requires N, 13·65; I, 41·3%).

The same compound resulted from the prolonged reaction between 2 : 3-dihydro-6-nitroglyoxalino[1 : 2-*a*]pyridine and methyl iodide in methanol and crystallised from methanol in short prisms, m. p. and mixed m. p. 246—247° (Found: N, 13·5; I, 41·4%).

Reaction of 2 : 3-*Dihydroglyoxalino*[1 : 2-*a*]*pyridine and Ethylene Dibromide*.—2 : 3-Dihydroglyoxalino[1 : 2-*a*]pyridine (1·4 g.) and ethylene dibromide (5 ml.) in ethyl methyl ketone (10 ml.) were heated under reflux for 1 hr., then cooled, and the solid which separated was collected and dissolved in the minimum amount of cold water. Acetone was slowly added to the solution until crystallisation ensued. After 12 hr. the solid was filtered off and recrystallised by the same procedure, giving *ethylene*-1 : 2-*bis*-1′-(2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium dibromide*) *dihydrate* (IX; *n* = 2) (900 mg.), m. p. 318—320° (slight sintering at 132°) (Found: C, 41·5; H, 5·0; N, 12·1; Br, 34·5; loss on drying at 100°, 7·0. $C_{16}H_{20}N_4Br_2,2H_2O$ requires C, 41·4; H, 5·2; N, 12·1; Br, 34·5; H_2O, 7·7%). The acetone–water mother-liquors were evaporated and the residue crystallised twice from propan-2-ol and finally from propan-2-ol–ethanol (2 : 1). 1-2′-*Bromoethyl*-2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium bromide* (V; R = H, R′ = X = Br) was obtained as needles, m. p. 186—189° (250 mg.) (Found: C, 35·5; H, 3·8; N, 9·1; Br, 51·7. $C_9H_{12}N_2Br_2$ requires C, 35·1; H, 3·9; N, 9·1; Br, 51·9%).

Under similar conditions, 2 mols. of 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine and 1 mol. of 1 : 3-dibromopropane gave *propylene*-1 : 3-*bis*-1′-(2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium dibromide*) *dihydrate* (IX; *n* = 3) which, crystallised from ethanol, had m. p. 156—157° (effervescence) (Found, after drying at 100°: N, 12·5; Br, 36·4. $C_{17}H_{22}N_4Br_2$ requires N, 12·5; Br, 36·2. Loss on drying, 7·3. $C_{17}H_{22}N_4Br_2,2H_2O$ requires H_2O, 7·5%).

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THE CHESTER BEATTY RESEARCH INSTITUTE, THE INSTITUTE OF CANCER RESEARCH: THE ROYAL CANCER HOSPITAL, FULHAM ROAD, LONDON, S.W.3.
CHEMICAL DIVISION, THE WELLCOME RESEARCH LABORATORIES, BECKENHAM, KENT.
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*The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part III.** 3 : 6-*Diaminoquinoxaline and Derived Compounds.*

By T. S. OSDENE and G. M. TIMMIS.

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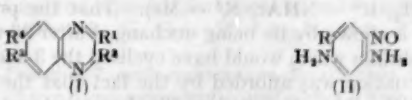
An unambiguous synthesis of **3** : **6**-diaminoquinoxaline, and its 2-carboxylic acid and amide, from **2** : 4-diamino-1-nitrosobenzene is described. The corresponding 7-methyl derivatives have also been prepared.

Acetylation of the 3-aminoquinoxaline-2-carboxyamides has been shown to give 3-acetamido-derivatives, which cyclise in dilute sodium hydroxide solution to **6** : 7-benzopteridines.

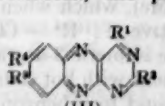
Four 2-aryl-substituted **3** : **6**-diaminoquinoxalines have been prepared from nitrosobenzene derivatives and phenylacetonitrile and its substituted derivatives.

QUINOXALINE (I; $R^1 = R^2 = R^3 = R^4 = H$) inhibits the growth of *S. lactis* R, the inhibition being reversed by folic acid (Hall, *Biochem. J.*, 1947, **41**, 294). Woolley and Pringle (*J. Biol. Chem.*, 1948, **174**, 327) found inhibition of *L. casei* in a quinoxaline derivative [I; $R^2 = R^3 = R^4 = H$, $R^1 = -CO{\cdot}NH{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}CH(CO_2H){\cdot}[CH_2]_2{\cdot}CO_2H$] which showed structural analogies with folic acid. Horner, Schwenk, and Junghanns (*Annalen*, 1953, **579**, 212) have recently prepared a number of quinoxalines, isosteric with simple pteridine derivatives. Further the successful use of sulphanilamide derivatives of quinoxalines as antibacterial agents in animals indicates the pharmacological suitability of this nucleus (Smith and Robinson, *Proc. Soc. Exp. Biol. Med.*, 1944, **57**, 292; Seeler *et al.*, *J. Pharmacol.*, 1944, **82**, 357). And since in Part I (*J.*, 1954, 2887) it was shown that 6-aryl-2 : 4 : 7-triaminopteridines showed antifolic acid activity we wished to ascertain the effect of analogous substitution in the quinoxaline nucleus.

Hitherto all routes leading to quinoxalines involve condensation of *o*-phenylenediamine with structures containing the 1 : 2-dicarbonyl function. Clearly when both the dicarbonyl structure and the *o*-phenylenediamine are unsymmetrically substituted, the product


(I)

(II)


(III)

isolated will be a mixture of isomers or a single substance of ambiguous structure. Thus a glyoxylic acid (or ester) or alloxan and an unsymmetrically substituted *o*-phenylenediamine will yield a 2(or 3)-hydroxyquinoxaline, or an alloxazine of undetermined structure. The former type of product has been converted into 2(or 3)-aminoquinoxalines by replacement of hydroxyl by chlorine and reaction with ammonia (Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1944, **66**, 1951; Wolf *et al.*, *ibid.*, 1949, **71**, 6); and the alloxazine by hydrolytic fission of the pyrimidine ring yields aminoquinoxalinecarboxylic acid or its derivatives (Kuhn and Bär, *Ber.*, 1934, **67**, 898; Weijlard and Tishler, U.S.P. 2,479,443;

* Part II, *J.*, 1954, 2895.

Wolf, Beutel, and Stevens, *J. Amer. Chem. Soc.*, 1948, **70**, 2572). Again, 2-aminoquinoxaline can be prepared by the condensation of *o*-phenylenediamine and formaldehyde cyanohydrin, ring closure of the product, and subsequent oxidation (Pfister, Sullivan, Weijlard, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4955), but ambiguous structures would be obtained from unsymmetrically substituted *o*-phenylenediamines.

We have therefore developed an unambiguous synthesis for 3 : 6-diaminoquinoxalines, both substituted and unsubstituted in the 2-position. We reported (*Chem. and Ind.*, 1954, 405) that *o*-aminonitrosobenzene derivatives react with cyanoacetic acid or its amide to yield quinoxaline derivatives. Part I (*loc. cit.*) described the formation of 6-aryl-7-aminopteridines from aminonitrosopyrimidines and substituted phenylacetonitriles and this reaction has now been extended to the preparation of several new 3 : 6-diamino-2-arylquinoxalines.

Readily available starting materials were 2 : 4-diamino- and 2 : 4-diamino-5-methyl-1-nitrosobenzene (II; R = H and Me) obtained by the nitrosation of *m*-phenylenediamine and *m*-tolylenediamine in hydrochloric acid solution with less than the theoretically required amount of sodium nitrite (Täuber and Walder, *Ber.*, 1900, **33**, 2118). On the reaction of (II; R = H or Me) with cyanoacetic acid in ethanol containing 2 mols. of sodium ethoxide, sodium 3 : 6-diaminoquinoxaline- and 3 : 6-diamino-7-methylquinoxaline-2-carboxylate (I; $R^2 = R^3 = NH_2$, R^4 = H or Me, $R^1 = CO_2Na$) were rapidly deposited in high yield. Lower yields were obtained when 1—2 mols. of sodium ethoxide were used. With 2-ethoxyethanol containing sodium 2-ethoxyethoxide there is more rapid reaction but greater contamination of the products. Both the quinoxalinecarboxylic acids were readily decarboxylated in hot quinoline. Both the resultant amines with hot acetic anhydride yielded the 3 : 6-diacetamido-derivatives.

2 : 4-Diamino-1-nitrosobenzene (II; R = H) with cyanoacetamide in ethanol containing 1 mol. of sodium ethoxide yielded 3 : 6-diaminoquinoxaline-2-carboxyamide (I; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3 = NH_2$, R^4 = H), which with boiling acetic anhydride yielded the same compound, 3 : 6-diacetamidoquinoxaline-2-carboxyamide (I; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3$ = NHAc, R^4 = H) after boiling for one or for sixty min. Warming this diacetamido-derivative in 0·5N-sodium hydroxide suspension caused rapid ring closure to 3′-acetamido-4-hydroxy-2-methyl-6 : 7-benzopteridine (III; $R^1 = OH$, $R^2 = Me$, $R^3 = NHAc$, R^4 = H). The diamino-amide with ethyl orthoformate in the presence of acetic anhydride (Albert, Brown, and Cheeseman, *J.*, 1951, 474) yielded a product to which structures (III; $R^1 = OH$, R^2 = H or Me, R^3 = NHAc or NH·CHO, R^4 = H) could be allotted, essentially depending on whether the 3-amino-group of the quinoxaline was acetylated or formylated before ring closure occurred. Hydrolysis of the cyclised product yielded 3′-amino-4-hydroxy-6 : 7-benzopteridine (III; $R^1 = OH$, $R^2 = H$, $R^3 = NH_2$, R^4 = H), showing that the initial compound must be 3′-acetamido-4-hydroxy-6 : 7-benzopteridine (III; $R^1 = OH$, $R^2 = H$, $R^3 = NHAc$, R^4 = H).

2 : 4-Diamino-5-methyl-1-nitrosobenzene (II; R = Me) and cyanoacetamide yielded 3 : 6-diamino-7-methylquinoxaline-2-carboxyamide (I; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3 = NH_2$, R^4 = Me), which when boiled with acetic anhydride for 1 min. yielded the 6-acetamido-derivative (I; $R^1 = CO{\cdot}NH_2$, $R^2 = NH_2$, $R^3 = NHAc$, R^4 = Me). That the product is not the isomeric 3-acetamido-derivative is shown by its being unchanged after 30 minutes' treatment with hot sodium hydroxide solution which would have cyclised the 3-acetamido-compound to a benzopteridine. Confirmation was afforded by the fact that the original amide (I; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3 = NH_2$, R^4 = Me) was readily diazotised and coupled with R salt, while the acetylated product was unaffected. It was to be expected that the aromatic 6-amino-group would be diazotised rather than the 3-amino-group in the pyrazine ring and this is shown to be the case by the inability of the 3-amino-group in the compound (I; $R^1 = CO{\cdot}NH_2$, $R^2 = NH_2$, $R^3 = NHAc$, R^4 = Me) to react with nitrous acid. Reaction of the amide (I; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3 = NH_2$, R^4 = Me) with boiling acetic anhydride for 1 hr. yielded the 3 : 6-diacetamidoamide together with a small amount of material $C_{16}H_{17}O_4N_5$, m. p. 245°. The structure (III; $R^1 = OAc$, $R^2 = R^4 = Me$, R^3 = NHAc), as the monohydrate, for this compound is supported by its infrared spectrum: in chloroform two absorption bands of approximately equal intensity were found in the

carbonyl region at 1679 and 1719 cm.$^{-1}$ and have been assigned to the secondary amide and the acetoxy-group respectively, and the total integrated intensity is close to that expected for these two groups (Richards and Burton, *Trans. Faraday Soc.*, 1949, **45**, 874; Jones, Ramsay, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80); the intensity evidence excludes, in particular, the structure (I; R^1 = CO·NHAc, R^2 = R^3 = NHAc, R^4 = Me) which would absorb much more strongly in this region. No weight loss occurred on drying *in vacuo* at 180°; Gowenlock, Newbold, and Spring (*J.*, 1948, 517) suggested an analogous structure for one of the products from the reaction of 2-aminoquinoxaline-3-carboxyamide (I; R^1 = CO·NH_2, R^2 = NH_2, R^3 = R^4 = H) with acetic anhydride. Prolonged treatment of the diacetamido-derivative (I; R^1 = CO·NH_2, R^2 = R^3 = NHAc, R^4 = Me) with hot acetic anhydride yielded exclusively the material, m. p. 245°. Ring closure of the diacetamido-derivative (I; R^1 = CO·NH_2, R^2 = R^3 = NHAc, R^4 = Me) with warm dilute sodium hydroxide solution yielded 3′-acetamido-4-hydroxy-2 : 2′-dimethyl-6 : 7-benzopteridine (III; R^1 = OH, R^2 = R^4 = Me, R^3 = NHAc) which however remains unchanged by boiling acetic anhydride for 9 hr.

2 : 4-Diamino-1-nitrosobenzene (II; R = H) also reacted with *o*-chlorophenylacetonitrile and *p*-chlorophenylacetonitrile in ethanol containing sodium ethoxide to yield 3 : 6-diamino-2-*o*- and 3 : 6-diamino-2-*p*-chlorophenylquinoxaline (I; R^1 = Cl·C_6H_4, R^2 = R^3 = NH_2, R^4 = H) respectively. Similarly 2 : 4-diamino-5-methyl-1-nitrosobenzene with phenylacetonitrile and *o*-chlorophenylacetonitrile yielded 3 : 6-diamino-7-methyl-2-phenyl- and -2-*o*-chlorophenyl-quinoxaline.

Experimental

M. p.s were determined on an electrically heated copper block. Analyses are by Mr. P. R. W. Baker, Beckenham. Fluorescence (which was intense) refers to ultraviolet light. Temperatures in parentheses in analyses refer to drying *in vacuo*.

3 : 6-*Diaminoquinoxaline-2-carboxylic Acid*.—To a solution of sodium (0·5 g.) in 2-ethoxyethanol (25 ml.) were added 2 : 4-diamino-1-nitrosobenzene (1·37 g.) and cyanoacetic acid (0·95 g.), and the mixture was boiled under reflux for 15 min., during which a brown precipitate was deposited. This (2·2 g.) was crystallised several times from acetic acid, to yield 3 : 6-*diaminoquinoxaline-2-carboxylic acid* as yellow rods, m. p. 255° (effervescence) [Found (110°): C, 52·1; H, 4·0; N, 27·6. $C_9H_8O_2N_4$ requires C, 52·9; H, 3·95; N, 27·4%]. The acetic acid solution showed an intense green fluorescence.

3 : 6-*Diaminoquinoxaline*.—3 : 6-Diaminoquinoxaline-2-carboxylic acid (1·33 g.) was boiled under an air-condenser with quinoline (50 ml.) for 30 min. during which a clear solution was obtained. The solution was filtered and the bulk of the quinoline was removed under reduced pressure on the pump. Addition of ether to the residue deposited a yellow precipitate, which after drying was sublimed twice at 180°/0·1 mm. Crystallisation from water yielded 3 : 6-*diaminoquinoxaline* as pale yellow silky needles, m. p. 204° (Found: C, 59·6; H, 4·9; N, 35·1. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%).

Treatment of the base with hot acetic anhydride yielded 3 : 6-*diacetamidoquinoxaline* as fine white needles (from water), m. p. 302° [Found (150°): C, 58·9; H, 5·1; N, 23·0. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·95; N, 22·9%].

The base and aqueous picric acid gave the *picrate*, orange rods (from water), m. p. 200° (decomp.) (Found: C, 43·4; H, 2·8; N, 24·6. $C_{14}H_{11}O_7N_7$ requires C, 43·2; H, 2·8; N, 25·2%).

3 : 6-*Diamino-7-methylquinoxaline-2-carboxylic Acid*.—2 : 4-Diamino-5-methyl-1-nitrosobenzene (3·0 g.) and cyanoacetic acid (2·0 g.) were added to a solution of sodium (1·2 g.) in ethanol (100 ml.), and the mixture was boiled under reflux for 1 hr. The precipitated salt was removed, washed with ether, and dried. Several crystallisations from glacial acetic acid yielded 3 : 6-*diamino-7-methylquinoxaline-2-carboxylic acid* as irregular yellow prisms, m. p. 248° (effervescence) (Found: C, 50·9; H, 5·3; N, 19·9. $C_{10}H_{10}O_2N_4.CH_3{\cdot}CO_2H$ requires C, 51·4; H, 5·75; N, 20·0%). The acetic acid solution showed a green fluorescence.

3 : 6-*Diamino-7-methylquinoxaline*.—3 : 6-Diamino-7-methylquinoxaline-2-carboxylic acid (1·0 g.) and nitrobenzene (10 ml.) were boiled under air-condenser for 1 hr. during which a clear solution was obtained. The hot solution was filtered through a warm funnel. Brown crystals were gradually deposited. After addition of ether and light petroleum (b. p. 40—60°) the crystalline precipitate was filtered off and dried (0·58 g.). Several crystallisations from water

yielded **3** : 6-*diamino*-7-*methylquinoxaline* as yellow rods, m. p. 221° (Found : C, 62·4; H, 5·9; N, 32·0. $C_9H_{10}N_4$ requires C, 62·05; H, 5·8; N, 32·2%).

Hot acetic anhydride (15 min.) yielded **3** : 6-*diacetamido*-7-*methylquinoxaline* as white silky needles, m. p. 310° (Found : C, 60·3; H, 5·55; N, 22·7. $C_{13}H_{14}O_2N_4$ requires C, 60·45; H, 5·5; N, 21·7%). **3** : 6-*Diamino*-7-*methylquinoxaline picrate* formed deep orange rods (from water), m. p. 288° (decomp.), softening at 250° (Found : C, 44·9; H, 3·4; N, 23·5. $C_{15}H_{12}O_7N_7$ requires C, 44·7; H, 3·25; N, 24·3%).

3 : 6-*Diaminoquinoxaline*-2-*carboxyamide*.—**2** : 4-Diamino-1-nitrosobenzene (2·74 g.) was added to a solution of sodium (0·15 g.) in ethanol (50 ml.), followed by cyanoacetamide (1·85 g.). The mixture was boiled under reflux for 5 min. during which a yellow precipitate was deposited. After chilling in ice-water the precipitate was removed and dried at 110° (yield, 3·5 g.). Several crystallisations from water (charcoal) yielded **3** : 6-*diaminoquinoxaline*-2-*carboxyamide* as yellow needles, m. p. 295° (decomp.) [Found (150°) : C, 53·4; H, 4·8; N, 34·5. $C_9H_9O_2N_5$ requires C, 53·2; H, 4·5; N, 34·5%]. The aqueous solution showed a yellowish-green fluorescence.

This amide (1·0 g.) gave a solution in boiling acetic anhydride (25 ml.) in 1 min., which then immediately deposited yellow crystals. The mixture was immediately chilled and the precipitate removed and dried (1·24 g.). Several crystallisations from *n*-butanol afforded **3** : 6-*diacetamidoquinoxaline*-2-*carboxyamide* as yellow heart-shaped plates showing a high degree of twinning, slowly softening above 260° [Found (180°) : C, 54·55; H, 4·3; N, 24·2. $C_{13}H_{13}O_4N_5$ requires C, 54·35; H, 4·55; N, 24·4%]. One hour's boiling gave identical material (crystal form; fluorescence) (Found : N, 24·4%). The solution in *n*-butanol showed a blue fluorescence.

3′-*Acetamido*-4-*hydroxy*-2-*methyl*-6 : 7-*benzopteridine*.—**3** : 6-Diacetamidoquinoxaline-2-carboxyamide (1·0 g.) was warmed in 0·5N-sodium hydroxide (40 ml.) until a clear solution was obtained (3—4 min.). The solution was filtered and acidified with glacial acetic acid, buff-coloured crystals being obtained. After cooling in ice-water, the precipitate was removed and dried (0·87 g.). Several crystallisations from *n*-butanol yielded 3′-*acetamido*-4-*hydroxy*-2-*methyl*-6 : 7-*benzopteridine* as small yellow rectangular rods, slow decomp. >280° [Found (180°) : C, 58·5; H, 4·6; N, 25·4. $C_{13}H_{11}O_3N_5$ requires C, 58·0; H, 4·1; N, 26·0%]. The solution in *n*-butanol showed a yellowish-green fluorescence.

3′-*Acetamido*-4-*hydroxy*-6 : 7-*benzopteridine*.—**3** : 6-Diaminoquinoxaline-2-carboxyamide (1·0 g.) was boiled under reflux with ethyl orthoformate (10 ml.) and acetic anhydride (10 ml.) for 2·25 hr. or 15 min. (Albert, Brown, and Cheeseman, *loc. cit.*). After cooling in ice, the precipitate was removed and dried (1·3 g.). Several crystallisations from dimethylformamide (charcoal) yielded 3′-*acetamido*-4-*hydroxy*-6 : 7-*benzopteridine* as orange platelets or stubby needles, m. p. >300° [Found (180°) : C, 56·05, 56·2; H, 3·75, 3·8; N, 27·0. $C_{12}H_9O_3N_5$ requires C, 56·5; H, 3·55; N, 27·4%]. The material was completely soluble in dilute sodium hydroxide solution and showed a salmon-pink fluorescence.

Hydrolysis of 3′-*Acetamido*-4-*hydroxy*-6 : 7-*benzopteridine*.—This amide (250 mg.) and 6N-hydrochloric acid (10 ml.) were boiled under reflux for 30 min., giving first a deep red solution and then a brown precipitate. After neutralisation with sodium carbonate solution, the precipitate was removed. Several crystallisations from water (some scarlet insoluble material was present) yielded 3′-*amino*-4-*hydroxy*-6 : 7-*benzopteridine* as deep orange needles, m. p. >340° [Found (180°) : C, 55·55; H, 3·7. $C_{10}H_7ON_5$ requires C, 56·3; H, 3·3%]. The alternative hydrolysis product, 3′-amino-4-hydroxy-2-methyl-6 : 7-benzopteridine, $C_{11}H_9ON_5$, would require C, 58·2; H, 4·0%.

The compound was easily soluble in dilute sodium hydroxide solution and this solution showed an orange fluorescence.

3 : 6-*Diamino*-7-*methylquinoxaline*-2-*carboxyamide*.—**2** : 4-Diamino-5-methyl-1-nitrosobenzene (6·0 g.) and cyanoacetamide (4·0 g.) were added to a solution of sodium (1·0 g.) in dry ethanol (150 ml.) and the mixture was boiled for 1 hr. A thick yellow precipitate was deposited after 30 min. After cooling in ice-water, the precipitate was removed (7·8 g.). Several crystallisations from water (charcoal) yielded **3** : 6-*diamino*-7-*methylquinoxaline*-2-*carboxyamide* as long yellow silky needles, m. p. 245° [Found (110°) : C, 55·8; H, 5·05; N, 32·4. $C_{10}H_{11}ON_5$ requires C, 55·3; H, 5·1; N, 32·2%]. The aqueous solution showed an intense green fluorescence. Diazotisation and coupling with R salt gave a brilliant scarlet colour.

6-*Acetamido*-3-*amino*-7-*methylquinoxaline*-2-*carboxyamide*.—**3** : 6-Diamino-7-methylquinoxaline-2-carboxyamide (1·0 g.) and acetic anhydride (25 ml.) were boiled under reflux for 1—2 min.; a bright yellow precipitate was formed. The mixture was immediately cooled in ice and the precipitate was washed with ether and dried in the air (1·1 g.). Several crystallisations from water (750 ml.) yielded 6-*acetamido*-3-*amino*-7-*quinoxaline*-2-*carboxyamide* as yellow

rectangular plates, m. p. 315° (slow decomp.) [Found (180°; loss, 7·1%) : C, 54·9; H, 4·6; N, 27·1. $C_{12}H_{13}O_2N_5$ requires C, 55·6; H, 5·05; N, 27·0; $C_{12}H_{13}O_2N_5,H_2O$ requires H_2O, 6·5%]. The aqueous solution showed a green fluorescence visible both in daylight and in ultraviolet light.

3 : 6-*Diacetamido-7-methylquinoxaline-2-carboxyamide*.—3 : 6-Diamino-7-methylquinoxaline-2-carboxyamide (4 g.) was boiled under reflux for 1 hr. with acetic anhydride (100 ml.). A bright yellow, thick precipitate was first formed which was rapidly transformed into a denser pale yellow material. After cooling in ice-water, the precipitate was washed with ether and dried in the air (3·84 g.). Two crystallisations from *n*-butanol afforded 3 : 6-*diacetamido-7-methylquinoxaline-2-carboxyamide* as yellow rods, m. p. >300° [Found (180°) : C, 55·8; H, 4·9; N, 23·0. $C_{14}H_{15}O_3N_5$ requires C, 55·8; H, 5·0; N, 23·25%].

The acetic anhydride mother-liquors were evaporated to dryness under reduced pressure to yield a pale yellow precipitate (0·74 g.). Several crystallisations from *n*-butanol afforded microscopic pale yellow needles, m. p. 244—245° [Found (110°) : C, 55·8; H, 4·8; N, 20·5. $C_{16}H_{17}O_4N_5$ requires C, 56·0; H, 5·0; N, 20·4%]. On the basis of the analysis and because in $CHCl_3$ infrared max. were found at 1719 (OAc) and 1679 (NHAc) cm.$^{-1}$ the tentative structure *3′-acetamido-4-acetoxy-2 : 2′-dimethyl-6 : 7-benzopteridine monohydrate* is assigned to this compound.

When the diacetamidoquinoxaline was boiled under reflux with acetic anhydride for a further 3 hr. it dissolved and, on working up, again yielded the material, m. p. 245°, which had a greenish-blue fluorescence.

3′-Acetamido-4-hydroxy-2 : 2′-dimethyl-6 : 7-benzopteridine.—3 : 6-Diacetamido-7-methylquinoxaline-2-carboxyamide (1·0 g.) was warmed in 0·5N-sodium hydroxide (40 ml.) until dissolved (3—4 min.). The solution was filtered and acidified with acetic acid, giving a pale buff-coloured precipitate. After cooling, this was removed (0·9 g.). Several crystallisations from a large volume of water yielded *3′-acetamido-4-hydroxy-2 : 2′-dimethyl-6 : 7-benzopteridine* as microscopic bundles of needles, m. p. >300° [Found (180°) : C, 59·6; H, 4·4; N, 24·8; O, 11·75. $C_{14}H_{13}O_2N_5$ requires C, 59·35; H, 4·6; N, 24·7; O, 11·30%]. The compound was easily soluble in sodium hydroxide solution which had an orange fluorescence. An acetic acid solution had a yellow fluorescence. The compound was unchanged by boiling acetic anhydride for 9 hr. [Found (180°) : C, 59·0; H, 4·85; N, 24·4; O, 11·9%].

3 : 6-*Diamino-2-o-chlorophenylquinoxaline*.—2 : 4-Diamino-1-nitrosobenzene (1·37 g.) and *o*-chlorophenylacetonitrile (1·6 ml.) were boiled under reflux for 4 hr. with a solution of sodium (0·3 g.) in ethanol (100 ml.). On cooling in ice, a crystalline material was deposited, which was removed (2·35 g.). Several crystallisations from 50% aqueous ethanol followed by one from ethanol yielded 3 : 6-*diamino-2-o-chlorophenylquinoxaline* as pale buff needles, m. p. 230—231° [Found (110°) : C, 61·3; H, 4·1; N, 20·6. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1; N, 20·7%]. The solution in ethanol showed a green fluorescence.

A similar mixture containing *p*-chlorophenylacetonitrile (1·6 ml.) was boiled for 1 hr. The bulk of the ethanol was removed and the residue was cooled in ice-water; a yellow precipitate was deposited (2·2 g.) which on several crystallisation from aqueous ethanol yielded 3 : 6-*diamino-2-p-chlorophenylquinoxaline* as yellow needles, m. p. 212—213° [Found (110°) : C, 62·2; H, 4·2; N, 21·2; Cl, 12·4. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1; N, 20·7; Cl, 13·1%]. The solution in ethanol showed a green fluorescence.

3 : 6-*Diamino-7-methyl-2-phenylquinoxaline*.—To a solution of sodium (0·3 g.) in dry ethanol (100 ml.) were added 2 : 4-diamino-5-methyl-1-nitrosobenzene (1·5 g.) and benzyl cyanide (1·2 ml.), and the mixture was boiled under reflux for 8 hr. After removal of the ethanol, the residue was triturated with water to give a buff precipitate, which was removed and dried in the air (2·25 g.). Several crystallisations from ethanol yielded 3 : 6-*diamino-7-methyl-2-phenylquinoxaline* as light brown plates, m. p. 174° [Found (110°) : C, 72·0; H, 5·5; N, 22·9. $C_{15}H_{14}N_4$ requires C, 72·0; H, 5·6; N, 22·4%]. The solution in ethanol showed a blue-green fluorescence.

3 : 6-*Diamino-2-o-chlorophenyl-7-methylquinoxaline*.—2 : 4-Diamino-5-methyl-1-nitrosobenzene (1·5 g.) and *o*-chlorophenylacetonitrile (1·6 ml.), reacting as above, gave 3 : 6-*diamino-2-o-chlorophenyl-7-methylquinoxaline* as colourless soft needles, m. p. 236° [Found (110°) : C, 63·1; H, 4·6; N, 19·9; Cl, 12·0. $C_{15}H_{13}N_4Cl$ requires C, 63·25; H, 4·6; N, 19·7; Cl, 12·45%]. The solution in ethanol showed a pale blue fluorescence.

CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH : ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3.

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The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part IV. 3 : 6-Diaminopyrido(2 : 3)pyrazines.†*

By T. S. Osdene and G. M. Timmis.

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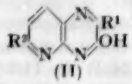
The unequivocal synthesis is reported of 3 : 6-diaminopyrido(2 : 3)pyrazine; † the 2-carboxylic acid and carboxyamide are obtained by the reaction of 2 : 6-diamino-3-nitrosopyridine with cyanoacetic acid and cyanoacetamide respectively. The alkali-hydrolysis product of the amide has been assigned the 3-amino-6-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid structure, since it differed from 6-amino-3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid, synthesised unambiguously from 2 : 6-diamino-3-nitrosopyridine with diethyl malonate. Seventeen aromatic and one heterocyclic derivative of acetonitrile have been treated with 2 : 6-diamino-3-nitrosopyridine, to give 2-substituted 3 : 6-diaminopyrido(2 : 3)pyrazines. Sodium alkoxides were effective catalysts for all the above condensations.

Owing to the close similarity of the pyrido(2 : 3)pyrazine nucleus (cf. I) to that of pteridine it was thought desirable to prepare a number of aminopyrido(2 : 3)pyrazines for biological testing. Only a few such compounds have been described, none of them containing an amino-group in the pyrazine nucleus. Most of those prepared have identical substituents in the 2- and the 3-position, being obtained by reaction of 2 : 3-diaminopyridine or its

(I)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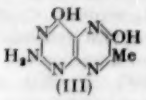
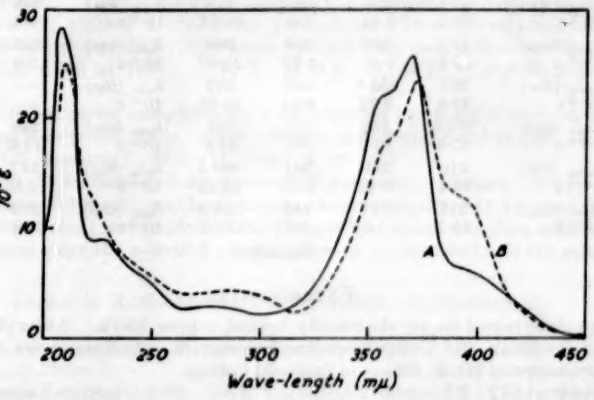

(III)

derivatives with a symmetrical 1 : 2-dicarbonyl compound (Tschitschibabin and Kirsanow, *Ber.*, 1927, **60**, 766; Bernstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1151; Lappin and Slezak, *ibid.*, 1950, **72**, 2806; Petrow and Saper, *J.*, 1948, 1389). Pyrido(2 : 3)-pyrazines unsymmetrically substituted in the 2- and the 3-position were prepared incidentally by Rudy and Majer (*Ber.*, 1938, **71**, 1323; 1939, **72**, 940) who condensed 2 : 3-diaminopyridine and 2-alkylamino-3-amino- and 3-amino-2-arylamino-pyridines with alloxan and claimed to have isolated 2-ureidopyrido(2 : 3)pyrazine derivatives and also 3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid (II; $R^1 = CO_2H$, $R^2 = H$); the only other example is Korte's condensation (*Chem. Ber.*, 1952, **85**, 1012) of 2 : 3-diamino- and 2 : 3 : 6-triamino-pyridine with pyruvic acid, which could yield either the 2-hydroxy-3- or the 3-hydroxy-2-methylpyrido(2 : 3)pyrazine derivative or both; the products were assigned the former structure, on the basis however only of the analogous synthesis of methylxanthopterin (III) from 2 : 5 : 6-triamino-4-hydroxypyrimidine and pyruvic acid (Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553). By extending the reactions of *o*-aminonitroso-compounds with cyanoacetic acid and amide (Osdene and Timmis, *Chem. and Ind.*, 1954, 405; and preceding paper) and with phenylacetonitrile derivatives (Spickett and Timmis, *J.*, 1954, 2887) to 2 : 6-diamino-3-nitrosopyridine we have synthesised a number of unambiguously orientated 3 : 6-diaminopyrido(2 : 3)pyrazine derivatives substituted in the 2-position by carbamyl and carboxyl groups and by aromatic and heterocyclic substituents.

2 : 6-Diaminopyridine was nitrosated in dilute acetic acid to give 2 : 6-diamino-3-nitrosopyridine (cf. Tschitschibabin and Seide, *J. Russ. Phys. Chem.*, 1918, **50**, 522) which was selected as the only readily available *o*-aminonitrosopyridine derivative which would yield products closely analogous to the biologically important pteridines containing a 2-amino-group in the pyrimidine ring. 2 : 6-Diamino-3-nitrosopyridine and cyanoacetic acid in

* Part III, preceding paper. † Named and numbered according to Ring Index No. 968.

2-ethoxyethanol containing 2 mols. of sodium 2-ethoxyethoxide gave sodium 3 : 6-diaminopyrido(2 : 3)pyrazine-2-carboxylate (I; R = CO_2Na). The acid was readily decarboxylated in boiling quinoline containing a little copper bronze, to yield 3 : 6-diaminopyrido(2 : 3)pyrazine (I; R = H) which was purified by sublimation and characterised also as the picrate and the 3 : 6-diacetamido-derivative. Similar reaction of the nitroso-compound with cyanoacetamide yielded 3 : 6-diaminopyrido(2 : 3)pyrazine-2-carboxyamide (I; R = CO·NH_2). This amide with ethyl orthoformate in the presence of acetic anhydride (cf. Albert, Brown, and Cheeseman, *J.*, 1951, 474) or with ethyl chloroformate alone (cf. Gowenlock, Newbold, and Spring, *J.*, 1948, 517) yielded yellow insoluble products which resisted purification. Alkaline hydrolysis of the amide (I; R = CO·NH_2) with boiling N-sodium hydroxide for 24 hours yielded a product, soluble in aqueous sodium



carbonate solution, whose analysis indicated its being either 3-amino-6- or 6-amino-3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid. This question was resolved by unambiguous synthesis of the latter acid (II; $R^1 = CO_2H$, $R^2 = NH_2$) from 2 : 6-diamino-3-nitrosopyridine and diethyl malonate.* The absorption spectrum of this acid in N-hydrochloric acid is shown as the curve *A*. The hydrolysis product of the amide (I; R = CO·NH_2) in N-hydrochloric acid gave the spectrum shown as curve *B*. Since the two curves are not identical, although the maxima and minima occur at very similar wavelengths the structure 3-amino-6-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid has been assigned to the hydrolysis product of the amide. Decarboxylation of the acid (II; $R^1 = CO_2H$, $R^2 = NH_2$) obtained from malonic ester yielded 6-amino-3-hydroxypyrido(2 : 3)pyrazine (II; $R^1 = H$, $R^2 = NH_2$), characterised as the acetyl derivative.

TABLE 1. *Absorption spectra of* 3 : 6-*diaminopyrido*(2 : 3)*pyrazines* (I) *in* N-*hydrochloric acid.*

R		(Approx.)									
H	$\lambda_{max.}$ (mμ)	208	249	295	364	382	$\lambda_{min.}$ (mμ)	238	269	313	371
	$10^{-3}\varepsilon$	30·4	5·7	3·04	25·3	28·3	$10^{-3}\varepsilon$	5·2	1·6	1·0	22·8
CO_2H	$\lambda_{max.}$ (mμ)	222	253·5	282	300	401	$\lambda_{min.}$ (mμ)	250	268	290	328
	$10^{-3}\varepsilon$	18·1	5·84	5·2	5·45	22·4	$10^{-3}\varepsilon$	5·77	4·6	5·0	8·0
CO·NH_2	$\lambda_{max.}$ (mμ)	213	255	280 *	303	400	$\lambda_{min.}$ (mμ)	247	288	328	—
	$10^{-3}\varepsilon$	27·4	8·2	5·6	6·6	27·7	$10^{-3}\varepsilon$	7·8	5·3	2·5	—

* Shoulder.

In the preparation of the 2-aryl derivatives, 2 : 6-diamino-3-nitrosopyridine was condensed with 17 different substituted phenylacetonitriles and with 2-thienylacetonitrile

* *Note added in Proof.*—After the submission of this paper, Leese and Rydon (*J.*, 1955, 304) published details of the preparation of 6-amino-3-hydroxypyrido(2 : 3)pyrazine and its 2-carboxylic acid by essentially the same method as that used by us.

in ethanol in the presence of sodium ethoxide to give 2-aryl-3 : 6-diaminopyrido(2 : 3)-pyrazines. The compounds which all had sharp melting points, were highly crystalline, and exhibited intense fluorescence in daylight and in ultraviolet light.

Ultraviolet absorption spectra are shown in Tables 1 and 2. Owing to the insolubility of most of these compounds in water and organic solvents, for determination of spectra the compounds were dissolved in 10N-hydrochloric acid and then diluted.

TABLE 2. *Absorption spectra of* 3 : 6-*diaminopyrido*(2 : 3)*pyrazines* (I) *in* N-*hydrochloric acid.*

R		(Approx.)							
p-F·C$_6$H$_4$	$\lambda_{max.}$ (mμ)	208·5	258	301	389	$\lambda_{min.}$ (mμ)	246	282	321
	10^{-3} ε	33·1	6·72	3·48	28·88	10^{-3} ε	5·95	2·8	2·2
o-MeO·C$_6$H$_4$	$\lambda_{max.}$ (mμ)	210	258	300 •	388	$\lambda_{min.}$ (mμ)	246	—	320
	10^{-3} ε	39·5	6·51	3·0	28·94	10^{-3} ε	5·6	—	2·0
m-MeO·C$_6$H$_4$	$\lambda_{max.}$ (mμ)	212	260	300	390	$\lambda_{min.}$ (mμ)	248	286	322
	10^{-3} ε	42·2	6·90	3·67	28·00	10^{-3} ε	5·8	3·3	2·4
p-MeO·C$_6$H$_4$	$\lambda_{max.}$ (mμ)	207	256 •	306	392	$\lambda_{min.}$ (mμ)	—	294	326
	10^{-3} ε	39·0	9·92	4·05	28·63	10^{-3} ε	—	4·0	3·2
p-NO$_2$·C$_6$H$_4$	$\lambda_{max.}$ (mμ)	207·5	258	—	393	$\lambda_{min.}$ (mμ)	249	—	314
	10^{-3} ε	33·6	12·2	—	33·9	10^{-3} ε	11·6	—	4·0
Ph	$\lambda_{max.}$ (mμ)	210	259	301	389·5	$\lambda_{min.}$ (mμ)	247	282	322
	10^{-3} ε	33·1	6·48	3·52	28·64	10^{-3} ε	5·6	2·9	2·25
2-Thienyl	$\lambda_{max.}$ (mμ)	215	267	315	398·5	$\lambda_{min.}$ (mμ)	259	293	335
	10^{-3} ε	25·3	7·8	4·6	27·8	10^{-3} ε	7·4	3·6	2·9

• Shoulder.

EXPERIMENTAL

M. p.s were determined in an electrically heated copper block. Absorption spectra were measured with Beckman and Uvispek spectrophotometers. Analyses were by Mr. P. R. W. Baker of Beckenham and Mr. F. Oliver of Imperial College.

3 : 6-*Diaminopyrido*(2 : 3)*pyrazine-2-carboxylic Acid.*—2 : 6-Diamino-3-nitrosopyridine (5·52 g.) and cyanoacetic acid (3·75 g.) were added to a solution of sodium (1·9 g.) in 2-ethoxyethanol (200 ml.) and the mixture was boiled under reflux for 30 min. The yellowish-brown precipitate was removed and purified by dissolution in boiling N-hydrochloric acid followed by neutralisation with dilute aqueous ammonia. Recrystallisation from water yielded 3 : 6-*diaminopyrido*(2 : 3)-*pyrazine-2-carboxylic acid* (4·4 g.) as yellow rods, m. p. 284° (decomp.) (Found, in material dried at 180° : C, 47·2; H, 3·1; N, 33·7. $C_8H_7O_2N_5$ requires C, 46·8; H, 3·4; N, 34·1%).

3 : 6-*Diaminopyrido*(2 : 3)*pyrazine.*—Finely ground 3 : 6-diaminopyrido(2 : 3)pyrazine-2-carboxylic acid (3·0 g.) was boiled under an air-condenser with quinoline (50 ml.) containing a trace of copper bronze. The clear solution obtained after 15 min. was filtered and concentrated. Treatment with ether and light petroleum (b. p. 40—60°) yielded a buff powder (2·34 g.). Sublimation at 220°/1 mm. yielded 3 : 6-*diaminopyrido*(2 : 3)*pyrazine* as a bright yellow powder, m. p. 238° (Found : C, 52·5; H, 4·7; N, 43·3. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·5%).

Alcoholic picric acid solution yielded the *picrate*, as orange irregular prisms, m. p. 260° (decomp.) (from aqueous ethanol) (Found : C, 40·5; H, 3·0; N, 28·8. $C_{13}H_{10}O_7N_8$ requires C, 40·0; H, 2·6; N, 28·7%).

Treatment of the diamine with hot acetic anhydride yielded 3 : 6-*diacetamidopyrido*(2 : 3)-*pyrazine* as silky needles (from water), m. p. 300° (Found : C, 54·2; H, 4·9; N, 28·6. $C_{11}H_{11}O_2N_5$ requires C, 53·9; H, 4·5; N, 28·6%).

3 : 6-*Diaminopyrido*(2 : 3)*pyrazine-2-carboxyamide.*—2 : 6-Diamino-3-nitrosopyridine (5·6 g.) and cyanoacetamide (3·7 g.) were boiled with a solution of sodium (0·6 g.) in ethanol (200 ml.) for 2 hr. The thick yellow precipitate obtained was purified by acid- and alkali-treatment and recrystallised from a large volume of water to yield 3 : 6-*diaminopyrido*(2 : 3)*pyrazine-2-carboxy-amide* (4·2 g.) as yellow needles, m. p. >300° (Found : C, 46·9; H, 4·16; N, 41·3. $C_8H_8ON_6$ requires C, 47·05; H, 3·95; N, 41·2%).

Hydrolysis.—The amide (1 g.) was boiled with N-sodium hydroxide (50 ml.) for 22 hr. The clear solution was filtered and acidified with acetic acid. The yellow precipitate obtained was dissolved in 2N-sodium carbonate and reprecipitated with acid. Recrystallisation from 80% formic acid yielded 3-*amino*-6-*hydroxypyrido*(2 : 3)*pyrazine-2-carboxylic acid* as clusters of yellow needles (Found : C, 46·6; H, 3·25; N, 27·5. $C_8H_6O_3N_4$ requires C, 46·6; H, 2·9; N, 27·2%).

6-Amino-3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic Acid.—2 : 6-Diamino-3-nitrosopyridine (4·14 g.) and diethyl malonate (5·3 g.) were boiled under reflux for 8 min. with a solution of sodium (1·3 g.) in 2-ethoxyethanol. The precipitate was removed, dissolved in boiling water, and recovered by hydrochloric acid. The yellow precipitate obtained was purified by several treatments with sodium carbonate or sodium hydroxide solution, followed by acidification, to yield *6-amino-3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid* as a yellow powder, m. p. >300° (Found, in material dried at 180°: C, 46·6; H, 3·1; N, 27·3. $C_8H_6O_3N_4$ requires C, 46·6; H, 2·9; N, 27·2%).

6-Amino-3-hydroxypyrido(2 : 3)pyrazine.—6-Amino-3-hydroxypyrido(2 : 3)pyrazine-2-carboxylic acid (0·8 g) was boiled with redistilled quinoline (10 ml.) for 1 hr., then was cooled and diluted with light petroleum (b. p. 40—60°), and the brown precipitate (0·64 g.) was removed and purified by dissolution in dilute sodium hydroxide solution (charcoal) followed by acidification with hydrochloric acid. The flocculent precipitate was dissolved by further addition of boiling water, and on cooling yielded a crystalline precipitate. Two recrystallisations from water yielded *6-amino-3-hydroxypyrido(2 : 3)pyrazine*, as very long pale yellow needles, m. p. >300° (Found, in material dried at 180°: C, 51·7; H, 3·6; N, 34·7. $C_7H_6ON_4$ requires C, 51·85; H, 3·7; N, 34·6%).

Treatment with hot acetic anhydride for 1 hr. afforded the *6-acetyl* derivative, pale yellow small needles (from *n*-butanol), m. p. >300° (Found, in material dried at 180°: C, 52·6; H, 4·2; N, 27·35. $C_9H_8O_2N_4$ requires C, 52·9; H, 3·95; N, 27·4%).

Preparation of 3 : 6-*Diamino-2-arylpyrido(2 : 3)pyrazines.*—Sodium (0·01 g.-atom) was dissolved in dry ethanol (100 ml.), and 2 : 6-diamino-3-nitrosopyridine (1·4 g.) and the appropriate arylacetonitrile (0·012 mol.) were added to the hot solution which was then refluxed for 1—4 hr. In some cases at this stage the pyrido(2 : 3)pyrazine was precipitated and the mixture was then cooled and filtered and the product recrystallised from the appropriate solvent. Alternatively the ethanol solution was reduced to small bulk, and the residue was diluted with water to precipitate the crude product which was then recrystallised. The *products* are reported in Table 3.

TABLE 3. 3 : 6-*Diamino-2-arylpyrido(2 : 3)pyrazines* (I).

				Found (%) §			Required (%)		
R	Form *	M. p.	Formula	C	H	N	C	H	N
Ph	Plates C	245°	$C_{13}H_{11}N_5$	65·5	4·7	29·6	65·8	4·7	29·5
p-F·C_6H_4	Needles A	284—285	$C_{13}H_{10}N_5F$	61·4	3·9	27·1	61·2	3·9	27·4
p-NO_2·C_6H_4	Rods † B	370 ‡	$C_{13}H_{10}O_2N_6$	55·3	3·8	30·0	55·3	3·6	29·8
o-Cl·C_6H_4	Prisms B	340	$C_{13}H_{10}N_5Cl$	57·5	3·9	25·4	57·5	3·7	25·8
m-Cl·C_6H_4	Prisms C	275—276	$C_{13}H_{10}N_5Cl$	57·4	3·8	26·1	57·5	3·7	25·8
p-Cl·C_6H_4	Rods C	274	$C_{13}H_{10}N_5Cl$	57·3	3·4	25·8	57·5	3·7	25·8
o-MeO·C_6H_4	Rods A	273	$C_{14}H_{13}ON_5$	62·8	5·0	25·9	62·9	4·9	26·2
m-MeO·C_6H_4	Plates A	205	$C_{14}H_{13}ON_5$	62·9	4·9	26·1	62·9	4·9	26·2
p-MeO·C_6H_4	Plates A	275	$C_{14}H_{13}ON_5$	62·8	5·1	26·4	62·9	4·9	26·2
o-EtO·C_6H_4	Prisms AC	290	$C_{15}H_{15}ON_5$	64·0	5·3	25·2	64·0	5·4	24·9
m-EtO·C_6H_4	Rods C	170	$C_{15}H_{15}ON_5$	64·7	5·4	25·0	64·0	5·4	24·9
p-EtO·C_6H_4	Plates C	256	$C_{15}H_{15}ON_5$	63·8	5·3	24·8	64·0	5·4	24·9
o-Me·C_6H_4	Rods B	332	$C_{14}H_{13}N_5$	67·2	5·4	27·6	66·9	5·2	27·9
α-$C_{10}H_7$	Plates D	259	$C_{17}H_{13}N_5$	70·2	4·95	24·4	71·1	4·6	24·4
β-$C_{10}H_7$	Rods C	256	$C_{17}H_{13}N_5$	70·95	4·2	24·5	71·1	4·6	24·4
3 : 4-$(MeO)_2C_6H_3$	Rods B	264	$C_{15}H_{15}O_2N_5$	61·1	4·8	23·45	60·6	5·1	23·6
3 : 4-$Cl_2C_6H_3$	Rods B	243	$C_{13}H_9N_5Cl_2$	50·5	3·1	23·0	51·0	3·0	22·9
2-Thienyl	Rods A	212—213	$C_{11}H_9N_5S$	54·0	3·7	28·6	54·3	3·7	28·8

* Letters refer to solvents: A, water; B, *n*-butanol; C, ethanol; D, ethyl acetate and light petroleum. All products were yellow except † orange.
‡ With decomp. § After drying at 110° *in vacuo*.

CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3.

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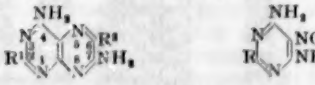
The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part V. 4 : 7-Diamino- and 2 : 4 : 7-Triamino-pteridine and its Derivatives.*

By T. S. Osdene and G. M. Timmis.

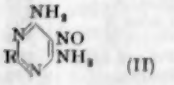
[Reprint Order No. 6035.]

Unequivocal syntheses of 4 : 7-diamino-, 2 : 4 : 7-triamino-, and 4 : 7-diamino-2-methylthiopteridine-6-carboxylic acids and their carboxyamides from 4 : 6-diamino-, 2 : 4 : 6-triamino-, and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidines with cyanoacetic acid and cyanoacetamide are reported. 4 : 7-Diamino- and 2 : 4 : 7-triamino-pteridine were obtained by decarboxylation of the corresponding acids. Sodium alkoxides were effective catalysts for the condensations.

In Part I (*J.*, 1954, 2887) an unequivocal synthesis of 6-aryl-7-aminopteridines was described, but only two pteridines have hitherto been reported which carried a 7-amino-group and were unsubstituted in the 6-position. One compound, 7-aminopteridine (Albert, Brown, and Wood, *J.*, 1954, 3832) was synthesised from 7-hydroxypteridine *via* the 7-mercapto-compound with subsequent amination, and the other, 7-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopteridine (Blicke and Godt, *J. Amer. Chem. Soc.*, 1954, **76**, 2798), by the reaction of 5 : 6-diamino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine with hydrogen cyanide and formaldehyde, followed by ring closure with potassium hydroxide in methanol and oxidation with hydrogen peroxide. In the latter compound the position of the amino-group is not conclusively proved. Since no 7-amino-6-arylpteridines examined disclosed outstanding anti-folic activity we wished to ascertain the effect of absence of the aryl substituent. By extending the reaction of *o*-aminonitroso-compounds with cyanoacetic acid and amide described by us (*Chem. and Ind.* 1954, 405) to the pyrimidine series we obtained 4 : 7-diamino- (I; $R^1 = R^2 = H$) and 2 : 4 : 7-triamino-pteridine (I; $R^1 = NH_2$, $R^2 = H$) and several of their derivatives.



(I)



(II)

4 : 6-Diamino-, 2 : 4 : 6-triamino-, and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine were readily prepared by nitrosation of the corresponding pyrimidines unsubstituted in the 5-position. 4 : 6-Diamino-5-nitrosopyrimidine (II; R = H) in boiling 2-ethoxyethanol containing 2 mols. of sodium 2-ethoxyethoxide with cyanoacetic acid yielded 4 : 7-diaminopteridine-6-carboxylic acid (I; $R^1 = H$, $R^2 = CO_2H$). Prolonged treatment of the acid with boiling quinoline caused decarboxylation to 4 : 7-diaminopteridine (I; $R^1 = R^2 = H$). Similarly the diamine (II; R = H) with cyanoacetamide under the same conditions gave 4 : 7-diaminopteridine-6-carboxyamide (I; $R^1 = H$, $R^2 = CO{\cdot}NH_2$). 2 : 4 : 6-Triamino-5-nitrosopyrimidine (II; $R = NH_2$) similarly afforded 2 : 4 : 7-triaminopteridine-6-carboxylic acid (I; $R^1 = NH_2$, $R^2 = CO_2H$) and its amide. Prolonged boiling of the acid in quinoline in the presence of copper bronze yielded a small amount of 2 : 4 : 7-triaminopteridine (I; $R^1 = NH_2$, $R^2 = H$) together with dark amorphous material, probably a decomposition product. Treatment of the triaminopteridinecarboxyamide with hot acetic anhydride yielded the triacetamido-derivative. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (II; R = MeS) gave 4 : 7-diamino-2-methylthiopteridine-6-carboxylic acid (I; $R^1 = MeS$, $R^2 = CO_2H$) and its amide. The latter with hot acetic anhydride yielded the diacetamido-derivative.

Ultraviolet absorption spectra of 4 : 7-diaminopteridine and the 6-carboxylic acid and its amide in acid solution are given in the Experimental section.

* Part IV, preceding paper.

Experimental

4 : 7-*Diaminopteridine-6-carboxylic Acid*.—4 : 6-Diamino-5-nitrosopyrimidine (3·2 g.) and cyanoacetic acid (2·0 g.) were added to a solution of sodium (1·1 g.) in 2-ethoxyethanol (200 ml.), and the mixture was boiled for 15 min. during which a thick brown precipitate was deposited. After filtration, the precipitate was acidified with acetic acid and the buff material thus obtained was recrystallised several times from water (charcoal), to yield **4 : 7-*diaminopteridine-6-carboxylic acid*** (2·1 g.) as yellow irregular plates, m. p. 292° (effervescence) (Found, in material dried at 180° : C, 41·2; H, 2·9; N, 40·0. $C_7H_6O_2N_6$ requires C, 40·8; H, 2·9; N, 40·8%). Absorption in 4½% $H{\cdot}CO_2H$: max. at 269 and 369 mμ (ε 21·4 and 11·3 × 10^3); min. at 302 mμ (ε 2·0 × 10^3).

4 : 7-*Diaminopteridine*.—**4 : 7**-Diaminopteridine-6-carboxylic acid (1·0 g.) was boiled with quinoline (25 ml.) for 1 hr. On cooling, a brown crystalline precipitate was deposited which was removed and washed with light petroleum (b. p. 40—60°). Several crystallisations from water (charcoal) yielded **4 : 7-*diaminopteridine*** as pale yellow needles, m. p. > 300° (Found, in material dried at 180° : C, 45·1; H, 3·4; N, 51·5. $C_6H_6N_6$ requires C, 44·5; H, 3·7; N, 51·8%). Absorption in 4½% $H{\cdot}CO_2H$: max. at 255, 285, and 343 mμ (ε 14·8, 4·4, and 12·5 × 10^3); min. at 272 and 300 mμ (ε 3·8, 3·8 × 10^3).

4 : 7-*Diaminopteridine-6-carboxyamide*.—To a solution of sodium (0·15 g.) in 2-ethoxyethanol were added **4 : 6**-diamino-5-nitrosopyrimidine (0·7 g.) and cyanoacetamide (0·85 g.), and the mixture was boiled under reflux for 2 min., during which a yellow precipitate was formed. After filtration the material was recrystallised from water to yield **4 : 7-*diaminopteridine-6-carboxyamide*** (0·87 g.), pale yellow needles, m. p. > 300° (Found : C, 40·8; H, 3·55; N, 46·1. $C_7H_7ON_7$ requires C, 41·0; H, 3·4; N, 47·3%). Absorption in 4½% $H{\cdot}CO_2H$: max. at 271 and 374 mμ (ε 22·7 and 10·6 × 10^3); min. at 304 mμ (ε 1·5 × 10^3).

2 : 4 : 7-*Triaminopteridine-6-carboxylic Acid*.—Finely powdered **2 : 4 : 6**-triamino-5-nitrosopyrimidine (4·62 g.) and cyanoacetic acid (2·8 g.) were heated in a solution of sodium (1·5 g.) in 2-ethoxyethanol (250 ml.) for 2½ hr. After cooling in ice, the yellowish-brown precipitate was removed and recrystallised from 30% formic acid. Further purification of the material by several dissolutions in dilute ammonia solution followed by reprecipitation with dilute acetic acid yielded **2 : 4 : 7-*triaminopteridine-6-carboxylic acid*** as needles, m. p. >300° (Found : C, 35·2; H, 3·75; N, 40·7. $C_7H_7O_2N_7,H_2O$ requires C, 35·15; H, 3·8; N, 41·0%).

2 : 4 : 7-*Triaminopteridine*.—**2 : 4 : 7**-Triaminopteridine-6-carboxylic acid (1·0 g.), redistilled quinoline (50 ml.), and a trace of copper bronze powder were boiled for 7 hr. The hot solution was filtered and on cooling deposited crystals (0·24 g.). Several crystallisations from very dilute ammonia solution yielded **2 : 4 : 7-*triaminopteridine*** as straw-coloured silky needles, m. p. > 300° (Found, in material dried at 150° : C, 41·3; H, 3·6; N, 55·3. $C_6H_7N_7$ requires C, 40·7; H, 4·0; N, 55·35%).

2 : 4 : 7-*Triaminopteridine-6-carboxyamide*.—**2 : 4 : 6**-Triamino-5-nitrosopyrimidine (3·0 g.) and cyanoacetamide (1·8 g.) were heated in a solution of sodium (0·5 g.) in 2-ethoxyethanol (200 ml.) for 5 min. A further 1 g. of cyanoacetamide was added and the mixture was boiled for another 5 min. The light brown crystalline precipitate was removed and extracted three times with boiling water. Crystallisation of the residue from dilute aqueous dimethylformamide yielded **2 : 4 : 7-*triaminopteridine-6-carboxyamide*** (2·1 g.), m. p. > 300° (Found, in material dried at 110° : C, 36·4, 36·2; H, 4·4, 4·2; N, 48·4, 48·2. $C_7H_8ON_8,\frac{1}{2}H_2O$ requires C, 36·3; H, 4·0; N, 48·4%). Treatment of the amide with hot acetic anhydride yielded the *triacetyl derivative* which was crystallised from aqueous dimethylformamide (Found, in material dried at 150° : C, 44·5; H, 4·3; N, 30·8. $C_{13}H_{14}O_4N_8,\frac{1}{2}H_2O$ requires C, 43·9; H, 4·3; N, 31·5%).

4 : 7-*Diamino-2-methylthiopteridine-6-carboxylic Acid*.—**4 : 6**-Diamino-2-methylthio-5-nitrosopyrimidine (1·84 g.) and cyanoacetic acid (1·0 g.) were boiled in a solution of sodium (1·0 g.) in ethanol (200 ml.) for 1 hr. The ethanol was removed and the residue was triturated with ether to give a solid material (2·4 g.) which was rapidly dissolved in boiling water (charcoal) and filtered. Acidification with dilute hydrochloric acid yielded a pink precipitate which was dissolved in hot dilute ammonia solution which was then acidified to pH 5. When scratched, the hot solution deposited unchanged nitroso-compound which was removed. The resulting yellow solution was acidified with an excess of glacial acetic acid, a pale yellow granular solid being obtained. The solid was purified by several precipitations from dilute ammonia with acetic acid to yield **4 : 7-*diamino-2-methylthiopteridine-6-carboxylic acid*** as pale yellow microscopic needles, m. p. > 300° (Found, in material dried at 150° : N, 33·2. $C_8H_8O_2N_6S$ requires N, 33·3%).

4 : 7-*Diamino*-2-*methylthiopteridine*-6-*carboxyamide*.—4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (0·9 g.) and cyanoacetamide (0·5 g.) were added to a solution of sodium (0·15 g.) in ethanol (100 ml.). Raising the mixture to the b. p. gave a clear solution which then deposited a yellow precipitate. After boiling for 2 min., the mixture was cooled and the precipitate removed. Recrystallisation from acetic acid followed by one crystallisation from *n*-butanol yielded **4 : 7-*diamino*-2-*methylthiopteridine*-6-*carboxyamide*** as light yellow needles, m. p. > 300° (Found, in material dried at 150° : C, 38·6; H, 3·9; N, 38·2; S, 12·3. $C_8H_9ON_7S$ requires C, 38·2; H, 3·6; N, 39·0; S, 12·7%). Treatment of the amide with hot acetic anhydride yielded the corresponding **4 : 7-*diacetamido*-**derivative (from dimethylformamide) (Found, in material dried at 150° : C, 43·5; H, 4·0. $C_{12}H_{13}O_3N_7S$ requires C, 43·0; H, 3·9%).

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CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH : ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, January 18th*, 1955.]

NOTES.

The Synthesis of 2 : 4-*Diamino*-7-*hydroxypteridine and its* 6-*Carboxylic Acid.*

By T. S. OSDENE and G. M. TIMMIS.

[Reprint Order No. 6036.]

2 : 4-DIAMINO-7-HYDROXYPTERIDINE, the 4-amino-analogue of *iso*xanthopterin, was required for biological testing. The derived 6-carboxylic acid was unambiguously synthesised from 2 : 4 : 6-triamino-5-nitrosopyrimidine and a large excess of diethyl malonate in boiling 2-ethoxyethanol containing 2 mols. of sodium 2-ethoxyethoxide (4 hr.). If equimolecular quantities of the reactants were used, reaction was incomplete after 14 hr. The acid was decarboxylated on sublimation in a high vacuum at 340° and yielded 2 : 4-diamino-7-hydroxypteridine.

Experimental.—**2 : 4-*Diamino*-7-*hydroxypteridine*-6-*carboxylic acid*.** 2 : 4 : 6-Triamino-5-nitrosopyrimidine (3·1 g.) and diethyl malonate (25 ml.) were added to a solution of sodium (1·0 g.) in 2-ethoxyethanol (200 ml.), and the mixture was boiled under reflux for 4 hr. After cooling, the yellow precipitate was removed and the mother-liquors were evaporated to dryness to yield more material. These were combined and dissolved in boiling water (alkaline to litmus), and the hot solution was filtered into an excess of boiling 2N-hydrochloric acid. The resulting yellow precipitate (2·5 g.) was purified several times by dissolution in hot 2N-sodium carbonate which was filtered into boiling hydrochloric acid to yield **2 : 4-*diamino*-7-*hydroxypteridine*-6-*carboxylic acid*** as a yellow powder, m. p. >360° (Found, in material dried at 180° : C, 38·2; H, 2·65; N, 37·6. $C_7H_6O_3N_6$ requires C, 37·8; H, 2·7; N, 37·8%). The acid solution of the acid showed an intense blue fluorescence, and gave a single blue fluorescent spot on a paper chromatogram when viewed in ultraviolet light. The absorption spectrum in 0·1N-sodium hydroxide showed max. at 350 (ε 14,900), 260 (ε 11,300), and 226 mμ (ε 38,000).

2 : 4-*Diamino*-7-*hydroxypteridine*. The acid (0·4 g.) was sublimed at 340—360°/0·05 mm. The pale yellow sublimate (0·25 g.) was purified by dissolution in dilute ammonia solution, filtration, and boiling off the ammonia. On cooling, **2 : 4-*diamino*-7-*hydroxypteridine*** was obtained as pale yellow needles, m. p. >300° (Found, in material dried at 180° : C, 40·6; H, 3·35; N, 47·7. $C_6H_6ON_6$ requires C, 40·45; H, 3·4; N, 47·2%). The solution in ammonia

showed an intense violet fluorescence, and gave a single blue fluorescent spot on a paper chromatogram when viewed in ultraviolet light. The absorption spectrum in 0·1N-sodium hydroxide showed max. at 341 (ε 14,100), 255 (ε 10,900), and 224 mμ (ε 40,300).

We thank Dr. E. M. F. Roe for the absorption spectra. This investigation has been supported by grants to this Hospital and Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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The Reaction of Triethyl Phosphite with Phenylmagnesium Bromide.

By (MISS) M. H. MAGUIRE and G. SHAW.

[Reprint Order No. 5971.]

GILMAN and VERNON (*J. Amer. Chem. Soc.*, 1926, **48**, 1063) showed that the reaction of triphenyl phosphite and an excess of phenylmagnesium bromide gave a 60% yield of triphenylphosphine and 68% of phenol. Gilman and Robinson later (*Rec. Trav. chim.*, 1929, **48**, 328) reported (although no experimental details are given) that the reaction of triethyl phosphite with an excess of phenylmagnesium bromide gave 10% of triphenylphosphine oxide Ph_3PO, and that a similar reaction with trimethyl phosphite afforded 42% of methyldiphenylphosphine oxide, which the authors suggested might arise from rearrangement of methyl diphenylphosphinite $Ph_2P{\cdot}OMe$ (cf. Arbuzov, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 395).

The present work arose out of a need for a suitable preparation of certain phosphonous acids $R{\cdot}P(OH)_2$ and it was considered, in view of the above results, that the reaction of a Grignard reagent with an excess of triethyl phosphite might provide a satisfactory route to them. Initially, equimolar amounts of triethyl phosphite and phenylmagnesium bromide were brought together in ether: from the mixture were isolated diphenyl (6·7%), triphenylphosphine oxide (14%), diphenylphosphinic acid Ph_2PO_2H (7·2%), and phenylphosphonous acid $Ph{\cdot}P(OH)_2$ (15·3%), and some triethyl phosphite was recovered. The formation of the required phosphonous acid in this reaction was promising, and accordingly a further reaction was carried out with a 2 : 1 molar ratio of the phosphite to the Grignard reagent; however, the same products, diphenyl (5·3%), triphenylphosphine oxide (10%), diphenylphosphinic acid (20·1%), and phenylphosphonous acid (5·8%), were isolated; in addition a small amount of a neutral compound (C, 66·6; H, 5·25%) was obtained to which no simple structure could be assigned, and almost 1 mol. of triethyl phosphite was recovered.

Experimental.—Phenylmagnesium bromide (1 mol., prepared from 26 g. of bromobenzene and 4 g. of magnesium) in ether (34 ml.) was added dropwise during 20 min. with shaking to triethyl phosphite (27·6 g.) in ether (40 ml.) at room temperature; heat was evolved and a colourless dense oil separated. The mixture was boiled under reflux for 30 min., cooled, and treated gradually with crushed ice (12 g.) and hydrochloric acid (20 ml.; 5N); the aqueous layer was washed with ether (30 ml.). The organic extracts were combined, washed with water (2 × 30 ml.), dried (Na_2SO_4) and evaporated to a pale yellow oil (12·7 g.); this was distilled to give a colourless liquid (6·5 g.), b. p. 150—162° (a mixture of triethyl phosphite, b. p. 155°, and bromobenzene, b. p. 155°); the residue was distilled *in vacuo* and afforded fractions: (i) a clear liquid (0·6 g.) with a garlic odour, b. p. 40—60°/5 mm., (ii) an oil (1 g.), b. p. 120—125°/5 mm., (iii) an oil (1 g.), b. p. 120°/1·5 mm., and (iv) an oil (2·5 g.), b. p. 210—230°/1·5 mm.; fractions (ii), (iii), and (iv) crystallised; fractions (ii) and (iii) were combined, and the solid was collected and recrystallised from ethanol–water, to give diphenyl (1·7 g.), m. p. and mixed m. p. 70—71°. The material from fraction (iv), triphenylphosphine oxide (2·3 g.), recrystallised from ethanol–water as laths, m. p. 156—157° (Found: C, 77·7; H, 5·4. Calc. for $C_{18}H_{15}OP$: C, 77·7; H, 5·45%); Kosolapoff (*J. Amer. Chem. Soc.*, 1942, **64**, 2982) gives m. p. 152—153°. The aqueous solutions were combined, diluted to 300 ml., and extracted with ether (3 × 50 ml.);

evaporation of the dried extract gave an oil (4·5 g.) which partly crystallised; the solid, diphenylphosphinic acid (1·3 g.), separated from ethanol–water as laths, m. p. 188° (Found: C, 65·9; H, 5·0. Calc. for $C_{12}H_{11}O_2P$: C, 66·05; H, 5·1%); Malatesta (*Gazzetta*, **1947**, **77**, **518**) gives m. p. 190°. The aqueous solution was made alkaline with sodium carbonate (*ca.* 22 g.), and the precipitated magnesium carbonate filtered off. The filtrate was concentrated to 200 ml. and acidified with hydrochloric acid, diphenylphosphinic acid (0·3 g.) separating; the filtrate was extracted with ether (4 × 50 ml.); evaporation of the dried extract gave diphenylphosphinic acid (1 g.). The aqueous solution was concentrated to 100 ml., an oil separating; this was extracted by ether (3 × 50 ml.), and evaporation of the solvent gave a crystalline solid; phenylphosphonous acid (3·6 g.) separated from carbon tetrachloride–acetone–light petroleum as prisms, m. p. 83—84° (Found: C, 50·7; H, 4·95%; equiv., 140·5. Calc. for $C_6H_7O_2P$: C, 50·45; H, 4·85%; equiv., 142); Kosolapoff (*J. Amer. Chem. Soc.*, 1950, **72**, 4291) gives m. p. 86°. The aqueous solution was finally evaporated to dryness and the solid residue was exhaustively extracted successively with ether and dry ethanol, but evaporation of the extracts gave in each case only a trace of gum.

We thank Dr. E. Challen for the microanalyses and the C.S.I.R.O. for a maintenance grant (to M. H. M.).

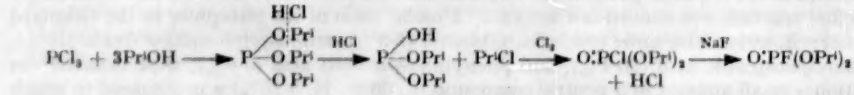
UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA. [*Received, December* 16*th*, 1954.]

Esters containing Phosphorus. Part XII. Esters of Phosphorofluoridic Acid.*

By H. GOLDWHITE and B. C. SAUNDERS.

[Reprint Order No. 5998.]

DI*iso*PROPYL PHOSPHOROFLUORIDATE has been prepared in good yield by a process depending upon the reactions outlined below (McCombie and Saunders, *Nature*, **1946**, **157**, 287; Saunders *et al.*, B.P. 601,210; Saunders and Stacey, *J.*, 1948, 695). American workers (U.S.P. 2,409,039) have similarly used the process starting with as much as 212 lb. of *iso*propanol. For small-scale work, however, chlorination of the hydrogen phosphite can be conveniently carried out by *N*-chlorosuccinimide; this method has the advantage that none of the products of the reaction is acidic (Kenner, Todd, and Weymouth, *J.*, 1952, 3675). We have shown that pure di*iso*propyl phosphorochloridate



can be obtained from di*iso*propyl hydrogen phosphite in 82% yield. It is also possible to prepare di*iso*propyl phosphorofluoridate without isolating the corresponding phosphorochloridate and thus the preparation can be run virtually as a " one-stage " process.

Di*cyclo*hexyl phosphorofluoridate is more toxic, and more stable to hydrolysis, than di*iso*propyl phosphorofluoridate. It is not easily obtained, however, by Saunders and Stacey's process, but we had prepared it by the action of phosphoryl dichlorofluoride on *cyclo*hexanol (Chapman and Saunders, *J.*, 1948, 1010): $POCl_2F + 2C_6H_{11}\cdot OH = (C_6H_{11}O)_2POF + 2HCl$. We have now shown that the action of *N*-chlorosuccinimide on di*cyclo*hexyl hydrogen phosphite followed by fluorination provides a convenient alternative preparation, and di*cyclo*hexyl phosphorofluoridate is now readily available. Most esters of phosphorofluoridic acid hitherto described in this series of papers can be prepared readily on a small scale in this way. Chlorination by *N*-chlorosuccinimide is more satisfactory than by sulphuryl chloride (Atherton, Howard, and Todd, *J.*, 1948, 1106) since an acid medium is produced by the latter reagent. By the former method it is possible to prepare phosphorofluoridates which contain unsaturated radicals, *e.g.*, diallyl phosphorofluoridate. In particular, compounds which decompose in the presence of acid on distillation are now easily obtained.

* Part XI, *J.*, 1953, 2115.

Experimental.—Diisopropyl phosphorochloridate. To a solution of diisopropyl hydrogen phosphite (0·1 mole) in dry carbon tetrachloride, *N*-chlorosuccinimide (0·1 mole) was added in portions of 0·5 g., with shaking and occasional cooling. The solution was then cooled to −5°, and the precipitated succinimide filtered off. Carbon tetrachloride was removed from the filtrate under reduced pressure, and the residue was fractionated. The product (17·5 g., 82%) boiled at 94—95°/14 mm. (McCombie, Saunders, and Stacey, *J.*, 1945, **380**, give b. p. 95°/14 mm.).

Cognate preparations of $(RO)_2POCl$.

R	Yield (%) from $P(OR)_3(OH)$	B. p./mm.	R	Yield (%) from $P(OR)_3(OH)$	B. p./mm.
Me	85%	54·5°/2	$CH_2{:}CH{\cdot}CH_2$ ...	38%	89—90°/0·9
Et	87·5%	93°/18	$-CHMe{\cdot}CO_2Et$ ...	75%	158—160°/1

Two procedures for the preparation of the esters of phosphorofluoridic acid were developed—a general one applicable to most alcohols and a special one adopted for *cyclo*hexanol.

Esters of phosphorofluoridic acid. (i) General procedure. To a vigorously stirred solution of the dry redistilled alcohol (0·3 mole) in dry carbon tetrachloride (30 ml.) a solution of redistilled phosphorus trichloride (0·1 mole) in carbon tetrachloride (20 ml.) was slowly added. After the addition, hydrogen chloride was expelled by refluxing the solution for 1 hr. and then by drawing dry air under reduced pressure through it for 2 hr. Solvent was added to replace that lost by evaporation, and the hydrogen phosphite was chlorinated by the addition in small portions (0·2 g.) of *N*-chlorosuccinimide (0·1 mole) with vigorous shaking and occasional cooling. The solution was then cooled to 5°, and the succinimide filtered off and washed with cold carbon tetrachloride. To the filtrate was added dry sodium fluoride (0·5 mole), and the mixture heated under reflux with vigorous stirring for 3 hr. The solids were filtered off, and the filtrate was dried (Na_2SO_4). Low-boiling liquids were removed by warming under reduced pressure. The residue was fractionated at low pressure in dry nitrogen to yield pure phosphorofluoridate.

Phosphorofluoridates, $(RO_2)_2POF$, *prepared as above.*

R	Yield (%) (from PCl_3 used)	B. p./mm.	F (%) * Found	F (%) * Calc.
Me	35	149—150°/760	14·70	14·82
Et	42	74·5—75·5/20	12·15	12·18
$CH_2F{\cdot}CH_2$	70	101—102/0·8	29·60	29·70
$CH_2Cl{\cdot}CH_2$	82	159—160/23	8·51	8·45
Pr^i	76	83/22	10·22	10·32
$CH_2{:}CH{\cdot}CH_2$	37	99—100/23	10·90	10·60
$Me{\cdot}CH(CO_2Et)$	47	128—130/1·0	6·60	6·33
$CHMe_2{\cdot}CH_2{\cdot}CHMe$	54·5	105—106/1·0	7·10	7·09

* The normal analytical procedure (Chapman, Heap, and Saunders, *Analyst*, 1948, **73**, 434—441) was used throughout except for difluoroethyl phosphorofluoridate (R = $CH_2F{\cdot}CH_2$). Here the method was modified by using enough sodium to provide 5-fold excess for the total fluorine content, and by refluxing the solution of the phosphorofluoridate and sodium ethoxide in ethanol for 3 hr. to ensure hydrolysis of the C–F as well as of the P–F links.

(ii) Di*cyclo*hexyl phosphorofluoridate. Phosphorus trichloride (13·75 g.) in carbon tetrachloride (20 ml.) was slowly added to dry distilled *cyclo*hexanol (30 g.). A stream of dry air was drawn through the solution during the addition to ensure thorough mixing and removal of hydrogen chloride. The solution was then heated under reflux for 1½ hr. and solvent and other low-boiling liquids were removed on a water-bath under reduced pressure and then at 100°/0·5 mm. The residual crude hydrogen phosphite was then dissolved in dry benzene (50 ml.) and chlorinated by addition of *N*-chlorosuccinimide (13·35 g.) in portions as described in the previous experiment. After cooling, the succinimide was filtered off, and the filtrate was heated to 60—70° with dry ammonium fluoride (18 g.) for 4 hr., with vigorous stirring. The product was shaken with water (100 ml.) and then twice with aqueous sodium hydroxide (50 ml.; 10%). The benzene solution was finally washed with water (2 × 50 ml.) and dried (Na_2SO_4). The benzene was removed under reduced pressure, and the residue fractionated in dry nitrogen, giving the pure di*cyclo*hexyl phosphorofluoridate (14 g., 52%), b. p. 125—128°/0·6 mm. (Found: F, 7·0. Calc. for $C_{12}H_{22}O_3FP$: F, 7·1%).

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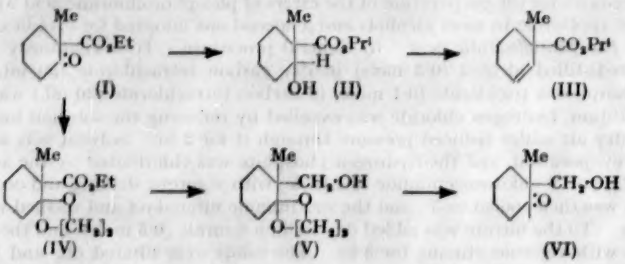
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 23rd*, 1954.]

Possible Intermediates for the Synthesis of Simple Analogues of Steroids.

By EDWARD R. CLARK and P. F. EPSTEIN.

[Reprint Order No. 51007.]

SOME reactions of the readily available ethyl 1-methyl-2-oxo*cyclo*hexane-1-carboxylate (I) have been examined with a view to the synthesis of simple analogues of biologically active steroids. Meerwein–Pondorf reduction yielded *iso*propyl 2-hydroxy-1-methyl*cyclo*hexane-1-carboxylate in 74% yield in 24 hr. [shorter periods yielded mixtures with the corresponding ethyl ester which was not readily separable by distillation (cf. Robinson and Walker, *J.*, 1937, **60**)]. The derived methoxy-ester gave the methoxy-acid on alkaline hydrolysis and the methoxy-alcohol on Bouveault–Blanc reduction.



The hydroxy-ester (II) was best (20%) converted into the *cyclo*hexene derivative (III) by treatment with phosphorus pentachloride in ether and subsequent heating with γ-collidine, which gave also a chlorine-containing compound believed to be essentially the chloro-ester though this could not be dehydrohalogenated by treatment with quinoline. The difficulty experienced in this dehydration and the comparative "stability" of the chloro-compound suggest some degree of rigidity in the ring structure preventing the adoption of the optimum conformation for ready elimination.

The *cyclo*hexene derivative (III) was readily brominated by *N*-bromosuccinimide. The crude product, which was not purified, did not yield the expected *iso*propyl 4-*p*-methoxyphenyl-1-methyl*cyclo*hex-2(or 3)-ene-1-carboxylate on treatment with *p*-methoxyphenylmagnesium bromide, but 47% of *iso*propyl 4-bromo-1-methyl*cyclo*hexene-1-carboxylate was isolated.

2-Hydroxymethyl-2-methyl*cyclo*hexanone (VI) has been prepared from our ester (I) *via* the ethylenedioxy-derivatives (IV and V) (cf. Buckta and Wolfrum, *Annalen*, 1953, **580**, 132): sodium and alcohol give yields of the alcohol (V) comparable with those obtained by using lithium aluminium hydride. The ethylenedioxy-group was hydrolysed by use of dilute phosphoric acid.

Experimental.—iso*Propyl* 2-*hydroxy*-1-*methyl*cyclo*hexane*-1-*carboxylate*. Ethyl 1-methyl-2-oxo*cyclo*hexane-1-carboxylate [Chatterjee and Roy, *J. Indian Chem. Soc.*, 1943, **20**, 329 (Found: C, 65·4; H, 8·7. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·7%); *semicarbazone*, m. p. 161° (Found: C, 54·7; H, 7·6; N, 16·7. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9; N, 17·4%)] (106·6 g.) and *iso*propyl alcohol (600 c.c.) were added to freshly prepared aluminium *iso*propoxide (120·4 g.), and the reduction carried out in the usual manner for 24 hr. The alcohol was distilled off under reduced pressure, the residue decomposed with a slight excess of hydrochloric acid, and the product extracted with ether. Distillation gave iso*propyl* 2-*hydroxy*-1-*methyl*cyclo*hexane*-1-*carboxylate* (86 g.), b. p. 108—110°/11 mm. (Found: C, 66·3; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%).

iso*Propyl* 2-*methoxy*-1-*methyl*cyclo*hexane*-1-*carboxylate*. The foregoing hydroxy-ester (20 g.) in sodium-dried ether (20 c.c.) was slowly added to powdered sodium (2·5 g.) in ether (100 c.c.), and the mixture heated on the steam-bath and stirred until all the sodium had reacted (2—3 hr.). Methyl iodide (17·1 g.) was added to the refluxing solution and the mixture stirred on the steam-bath for a further 3 hr. After filtration, distillation yielded the 2-*methoxy-ester* (13 g.), b. p. 97—102°/9—10 mm. (Found: C, 67·25; H, 10·45. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%).

2-Methoxy-1-methylcyclohexane-1-carboxylic acid. The methoxy-ester (50·8 g.), when heated on the steam-bath for 6 hr. with 10% alcoholic potassium hydroxide (200 c.c.), gave the *methoxy-acid* (22·5 g.), m. p. 89° (from 25% aqueous alcohol) (Found: C, 62·7; H, 9·2. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%), and, from the mother-liquors, *2-hydroxy-1-methylcyclohexane-1-carboxylic acid* (3·4 g.) (Found: C, 60·4; H, 9·2. $C_8H_{14}O_3$ requires C, 60·75; H, 8·85%).

1-Hydroxymethyl-2-methoxy-1-methylcyclohexane. Sodium (31·2 g.), in large pieces, was added as rapidly as possible to a solution of *iso*propyl 2-methoxy-1-methylcyclohexane-1-carboxylate (47·7 g.) in alcohol (400 c.c.), cooled in ice-water. The mixture was then stirred and heated on the steam-bath until dissolution of the sodium was complete (2—3 hr.). Water was added, the alcohol distilled off, and the resulting oil extracted with ether. Distillation yielded *1-hydroxymethyl-2-methoxy-1-methylcyclohexane* (20·8 g.), b. p. 97—103°/12 mm. (Found: C, 68·7; H, 11·7. $C_9H_{18}O_2$ requires C, 68·35; H, 11·4%). This gave a *p-nitrobenzoate*, m. p. 73—74° (Found: C, 62·85; H, 6·45; N, 4·55. $C_{16}H_{21}O_5N$ requires C, 62·55; H, 6·85; N, 4·55%).

Dehydration of isopropyl 2-hydroxy-1-methylcyclohexane-1-carboxylate. The hydroxy-ester (30 g.) was added during 25 min. to a stirred suspension of phosphorus pentachloride (32 g.) in dry ether (120 c.c.), at 0—10°. The mixture was heated under reflux for 1 hr., decomposed with ice, and extracted with ether in the usual manner. Distillation yielded a fraction, b. p. 80—115°/10 mm. (15 g.), which was heated at 160° for 10 min. with freshly distilled collidine. The cooled mixture was treated with dilute sulphuric acid and the oil extracted with ether. Distillation yielded *isopropyl 1-methylcyclohex-2-ene-1-carboxylate* (5·2 g.), b. p. 77—78°/11 mm. (Found: C, 72·2; H, 10·0. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%), and an oil (4·3 g.), b. p. 113/11 mm., consisting mainly of *iso*propyl 2-chloro-1-methylcyclohexene-1-carboxylate (Found: C, 61·8; H, 9·4; Cl, 14·95. Calc. for $C_{11}H_{19}O_2Cl$: C, 60·4; H, 8·7; Cl, 16·2%).

Poorer yields of the *cyclo*hexene (III) were obtained by using phosphorus tribromide and pyridine, and by distillation of the phosphate ester obtained by the action of phosphorus pentoxide on the alcohol. Potassium hydrogen sulphate and activated alumina both failed to effect the dehydration.

Bromination of isopropyl 1-methylcyclohex-2-ene-1-carboxylate and attempted Grignard reaction. The unsaturated ester (6·5 g.), *N*-bromosuccinimide (6·2 g.), and carbon tetrachloride (40 c.c.) were heated under reflux under nitrogen for 2½ hr., then filtered and evaporated. An ethereal solution (30 c.c.) of the residue, cooled in ice, was treated with *p*-methoxyphenylmagnesium bromide [from *p*-bromoanisole (6 g.) and magnesium (0·78 g.) in ether (20 c.c.)] during 2 hr. and the mixture stirred in ice for a further 30 min. Next morning, no Grignard reagent remained (test with Michler's ketone). Working up in the usual manner yielded *isopropyl 4-bromo-1-methylcyclohex-2-ene-1-carboxylate* (4·4 g.), b. p. 65—67°/0·1 mm. (Found: C, 50·35; H, 6·7; Br, 30·3. $C_{11}H_{17}O_2Br$ requires C, 50·6; H, 6·5; Br, 30·7%).

Ethyl 2 : 2-ethylenedioxy-1-methylcyclohexane-1-carboxylate. Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate (20 g.), ethylene glycol (8 g.), a crystal of toluene-*p*-sulphonic acid, and dry benzene (100 c.c.) were refluxed under a water-separator, until no more water separated (14 hr.). The benzene solution was washed with sodium carbonate solution, and water, and dried (Na_2SO_4). Distillation yielded the 2 : 2-ethylenedioxy-ester (22·3 g.), b. p. 136°/16 mm. (Found: C, 64·0; H, 8·9. Calc. for $C_{12}H_{20}O_4$: C, 63·15; H, 8·8%). Repeated redistillation failed to yield a pure product with a closer analysis for carbon: probably some ester interchange took place.

2 : 2-Ethylenedioxy-1-hydroxymethyl-1-methylcyclohexane. The foregoing ester (20 g.) was reduced with absolute alcohol (200 c.c.) and sodium (12·5 g.) as described above. The 2 : 2-ethylenedioxy-alcohol (14 g.), b. p. 136°/14 mm., was obtained (Found: C, 64·35; H, 9·6. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·75%).

1-Hydroxymethyl-1-methylcyclohexan-2-one. The foregoing alcohol (10 g.) was heated under reflux for 2 hr. with a 5% aqueous solution (35 c.c.) of syrupy phosphoric acid. Ether-extraction, etc., yielded 1-hydroxymethyl-1-methylcyclohexan-2-one (5·7 g.), b. p. 103—104°/11 mm. (Found: C, 67·7; H, 10·1. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·85%) [*2 : 4-dinitrophenylhydrazone*, m. p. 73° (Found: C, 52·2; H, 5·55; N, 17·7. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%)].

One of us (P. F. E.) acknowledges the receipt of a grant from the D.S.I.R. We are indebted to Mrs. Y. Richards and Miss M. Clarke of the Microanalytical Laboratory for the analyses.

THE UNIVERSITY, LEEDS. [*Received, December 28th*, 1954.]

Hydrazine. Part XI. N-Methyl-aldazinium and -ketazinium Chlorostannates derived from Methylhydrazine.*

By M. Lamchen and A. M. Stephen.

(Reprint Order No. 51017.)

It was shown in Part IX * that condensation of acetone with methylhydrazine in presence of hydrochloric acid and stannic chloride afforded the chlorostannate of *N*-methyldimethyl ketazine, not a pyrazolinium derivative as when hydrazine was used instead of methylhydrazine. We have extended this reaction by substituting ethyl methyl ketone, diethyl ketone, methyl *n*-propyl ketone, acetophenone, and a number of aldehydes for acetone, whereupon the corresponding *N*-methylaldazinium salts and one *N*-methylketazinium salt have been obtained.

The annexed Table indicates the nature of the chlorostannates formed by reaction of carbonyl compounds with methylhydrazine in methanol containing aqueous hydrochloric acid and a small excess of stannic chloride. The aldazinium salts crystallised readily within a few minutes in the cold, but the product obtained from ethyl methyl ketone

N-Methyl-aldazinium and -ketazinium chlorostannates, $[R{:}N{\cdot}\overset{+}{N}Me{:}R]_2SnCl_6^{2-}$.

Compound : * R =	M. p.	Formula	(Found %) Cl	(Found %) N	Required (%) Cl	Required (%) N
(1) CMeEt †	138—139°	$(C_9H_{19}N_2)_2SnCl_6$	33·2	8·8	33·2	8·7
(2) $C_6H_5{\cdot}CH$	205—206	$(C_{15}H_{15}N_2)_2SnCl_6$	27·1	7·0	27·4	7·2
(3) $C_6H_5{\cdot}CH{:}CH{\cdot}CH$	197 (decomp.)	$(C_{19}H_{19}N_2)_2SnCl_6$	23·8	6·7 ‡	24·15	6·4
(4) $p\text{-}C_6H_4(OMe){\cdot}CH$	215—216	$(C_{17}H_{19}O_2N_2)_2SnCl_6$	24·0	6·2	23·7	6·2
(5) 2 : 4-$C_6H_3(OH)_2{\cdot}CH$	*ca.* 230	$(C_{15}H_{15}O_4N_2)_2SnCl_6$	23·5	6·5 ‡	23·5	6·2
(6) 3 : 4-$C_6H_3(OMe)(OH){\cdot}CH$	*ca.* 180	$(C_{17}H_{19}O_4N_2)_2SnCl_6$	22·0	6·4 ‡	22·15	5·8
(7) 3 : 4-$C_6H_3(OMe)_2{\cdot}CH$	225 (decomp.)	$(C_{19}H_{23}O_4N_2)_2SnCl_6$	20·9	5·4 ‡	20·9	5·5

* Appearance : (1) Colourless squat prisms; (2)—(5) microcrystalline, and pale yellow, vermilion, bright yellow and deep yellow, respectively; (6) and (7) deep yellow powders; (5) and (6) became blood-red in conc. aq. NaOH, forming a yellow solution on dilution.

† Reactants heated for 15 min. under reflux.

‡ Estimated by Dumas's method; compound not decomposed quantitatively by boiling with aqueous hydrochloric acid.

separated from solution only after storage for one week at −10°. No satisfactory compounds could be prepared from acetaldehyde, propaldehyde, crotonaldehyde, or the ketones, other than ethyl methyl ketone, named above. When salicylaldehyde was used, salicylaldazine methochloride was precipitated instead of the corresponding chlorostannate; its ease of formation is unexpected in view of difficulties encountered in preparing salicylaldazine hydrochloride (Mrs. E. G. Sohn, personal communication; cf. Part X, *loc. cit.*).

In general, the salts are hydrolysed readily in aqueous acid solution, forming the aldehyde or ketone, as shown by reaction with 2 : 4-dinitrophenylhydrazine. Gelatinous tin hydroxide is formed when the chlorostannates are boiled with water. Although the products from vanillin and veratraldehyde dissolved in dilute hydrochloric acid, the aldehydes could not be driven out by evaporating the solution to small bulk; on cooling, the aldazinium salts were reprecipitated.

The observation (Part IX) that the use of phenylhydrazine in place of hydrazine gave, with boiling acetone, hydrochloric acid, and stannic chloride, an *N*-substituted pyrazolinium chlorostannate led us to repeat this reaction with other ketones: ethyl methyl, methyl *n*-propyl, and di-*n*-propyl ketone afforded substituted indoles and ammonium chlorostannate, and methyl *iso*propyl and di*iso*propyl ketone gave the indoleninium and ammonium chlorostannates.

Experimental.—Methods of analysis were as described in Parts VI and X (*locc. cit.*). The nitrogen values given in the Table were calculated from the methylhydrazine content where this could be determined; combustion (Dumas) was resorted to if the salt was not completely decomposed by dilute acid.

* Parts VI, IX, and X, *J.*, 1953, 3445; 1954, 2429; 1955, 1753.

Methylhydrazine hydrochloride, prepared from the sulphate, crystallised from methanol as glistening prisms, m. p. 137° (sintering at 131°) (Found, in material dried at 80° *in vacuo*: Cl, 52·9; CH_6N_2, 45·5. Calc. for $CH_6N_2,HCl + CH_6N_2,2HCl$: Cl, 53·0; CH_6N_2, 45·7%).

Salicylaldazine Methochloride.—Addition of salicylaldehyde (4 c.c.) in methanol to methylhydrazine (0·3 g.) in methanol containing a small excess of aqueous hydrochloric acid caused precipitation within a few minutes of the above *methochloride* as canary-yellow, glistening plates, m. p. 204° (decomp.) (Found, on material dried at 80° *in vacuo*: Cl, 12·1; CH_6N_2, 15·4. $C_{15}H_{15}O_2N_2Cl$ requires Cl, 12·2; CH_6N_2, 15·8%). The same compound was formed when stannic chloride (0·2 c.c.) was added before the salicylaldehyde. The methochloride became deep-red in contact with concentrated aqueous alkali, the colour changing to yellow on dilution with water.

Bis-(2 : 3 : 3-trimethylindoleninium) hexachlorostannate. To phenylhydrazine hydrochloride (3·7 g.) in methyl *iso*propyl ketone (30 c.c.) were added stannic chloride (2 c.c.) and concentrated hydrochloric acid (1 c.c.), and the solution was heated on the water-bath under reflux. Colourless crystals were deposited within 20 min., and after 7 hr. the mixture was cooled and the solid (7·0 g.) collected. Recrystallisation from dilute hydrochloric acid removed ammonium chlorostannate and afforded the above-named *salt* as nearly white prisms, m. p. 229° [Found, in material dried at 100° *in vacuo*: Cl, 32·6; N, 4·2. $(C_{11}H_{14}N)_2SnCl_6$ requires Cl, 32·65; N, 4·3%]. When a solution of the chlorostannate was made alkaline, the base was liberated; this was characterised as the picrate, m. p. 161° (lit. 158°).

*Bis-(3 : 3-dimethyl-2-iso**propyl**indoleninium) hexachlorostannate.* By an essentially similar method di*iso*propyl ketone afforded crystals of ammonium chlorostannate embedded in a viscous yellow oil. The mixture was made alkaline and steam-distilled, yielding 3 : 3-dimethyl-2-*iso*propylindolenine after extraction of the steam-distillate with light petroleum (b. p. 40—60°); this was converted in the usual way into a *chlorostannate*, which formed prisms, m. p. 174° (red melt) after recrystallisation from dilute hydrochloric acid [Found, in material dried at 80° *in vacuo*: Cl, 30·0; N, 4·3. $(C_{13}H_{18}N)_2SnCl_6$ requires Cl, 30·1; N, 4·0%]. Both the indolenine and the salt were identical with samples prepared by Plancher's method (*Ber.*, 1898, **31**, 1498) from di*iso*propyl ketone phenylhydrazone.

UNIVERSITY OF CAPE TOWN. [*Received, December 30th*, 1954.]

Some Reactions of cyclo*Propane, and a Comparison with the Lower Olefins. Part II.* Some Platinous–*cyclo*Propane Complexes.*

By C. F. H. TIPPER.

[Reprint Order No. 6013.]

OLEFINS act as ligands in complexes with silver, cuprous, mercuric, and platinous salts (Keller, *Chem. Rev.*, 1941, **28**, 229). If the *cyclo*propane ring has some double-bond character, this compound might possibly form similar complexes. Solid silver nitrate, mercuric acetate, and cuprous chloride showed no evidence of complex formation in the presence of liquid *cyclo*propane at room temperature (cf. propylene; Francis, *J. Amer. Chem. Soc.*, 1951, **73**, 3709). However, when a dilute solution of chloroplatinic acid in acetic anhydride was treated with *cyclo*propane at room temperature, roughly four moles of gas per mole of acid were very rapidly absorbed, and a brown solid separated which gave reactions to be expected of a platinous–*cyclo*propane complex. When propylene was used, only platinous chloride was precipitated, and when shaken with aqueous potassium chloroplatinite *cyclo*propane was absorbed very slowly if at all.

The brown powder, dried *in vacuo*, rapidly absorbed up to ~4% of its weight of water from the atmosphere, but no more. It was very slightly soluble in water, the suspension being acid and titratable with sodium hydroxide solution. When it was boiled with water, platinum was rapidly formed. Addition of cold aqueous potassium cyanide led to a brisk evolution of *cyclo*propane. The solid dissolved in warm (~60°) pyridine or styrene, gas being evolved, and in quinoline to give a red-brown solution. It dissolved slowly in 10N-hydrochloric acid, and was moderately soluble in ethyl alcohol and slightly soluble in

* Part I, *J.*, 1955, 713.

ether, acetone, chloroform, and carbon tetrachloride. On separation from the organic liquid a substance of empirical formula $PtCl_2,C_3H_6$ was obtained. By analogy with the olefin complexes the molecular formula is presumably $(PtCl_2,C_3H_6)_2$. Analysis of the brown powder, together with the acid nature of its aqueous suspension, gives some indication that it is a mixture of the above complex with $HPtCl_3,C_3H_6,H_2O$ (analogous to Zeise's acid). However, it has not been possible to isolate this compound, if, indeed, it exists.

The reaction of pyridine and the "mixture" *in vacuo* gave a white compound $(C_5H_5N)_2PtCl_2,C_3H_6$. This decomposed in boiling water to give platinum, and dissolved in warm 10N-hydrochloric acid, but appeared to be more stable than the other two complexes in that potassium cyanide solution at 30—40° released *cyclo*propane only slowly, and no gas was evolved with warm pyridine, styrene, or aqueous sodium nitrite.

The fact that only *cyclo*propane was evolved when the complexes were treated with cyanide strongly suggests that the three-membered ring is intact in these molecules. The infrared spectrum of *cyclo*propaneplatinous chloride includes two very strong peaks at 3·27 and 3·35 μ, which might be *cyclo*propane C–H vibration bands shifted slightly from 3·23 and 3·32 μ (Stabley, *J. Amer. Chem. Soc.*, 1954, **76**, 3604) owing to complex formation. The existence of only two C–H absorptions, if not due to inadequate resolution by the spectrometer, suggests that the platinum atom is bound equally to all three carbon atoms.* However, whatever their detailed molecular structure, the actual existence of these substances strongly supports the view of both Walsh (*Trans. Faraday Soc.*, 1949, **45**, 179) and of Coulson and Moffitt (*Phil. Mag.*, 1949, **40**, 1) that there is considerable delocalisation of the electrons of the *cyclo*propane ring.

Experimental.—(Microanalyses were by Mr A. S. Inglis, of the Department of Organic Chemistry.)

*cyclo*Propane (from a cylinder) was passed for 2 hr. through a solution of commercial "platinum chloride" (1 g.) in 15—20 ml. of "AnalaR" acetic anhydride; the red colour soon darkened and a brown powder began to be precipitated. The whole was left overnight, and the precipitate filtered off, washed with acetic anhydride, and dried *in vacuo* (yield 0·1—0·15 g.) [Found: Pt (ash), 57·8; C, 11·1; H, 2·3; Cl, 25·0. Calc. for $C_3H_8OCl_2Pt$: Pt, 53·8; C, 9·9; H, 2·5; Cl, 29·3%. Calc. for $C_3H_4Cl_2Pt$: Pt, 63·3; C, 11·7; H, 2·0; Cl, 23·0%]. The powder decomposed during several months, going grey-green ($PtCl_2$) and then black. Addition of aqueous potassium cyanide *in vacuo* gave a gas condensable in liquid nitrogen. It burned over copper oxide to give approx. 3 vols. of carbon dioxide, and was completely absorbed by 85% sulphuric acid but unaffected by a solution of mercuric sulphate in 22% sulphuric acid. The gas was therefore *cyclo*propane (*e.g.*, see Brooks, Murdock, and Zahn, *Analyt. Chem.*, 1948, **20**, 62).

cyclo*Propaneplatinous chloride*. The dried product from the above preparation was shaken with 2—3 ml. of acetone–ether (1 : 1), and the solid collected, washed with 1—2 ml. of the liquid, then with acetic anhydride, and dried *in vacuo*. The *product* was obtained as a very light brown powder which absorbed traces of water from the atmosphere. It decomposed, without melting, above 100° [Found: Pt, 61·8; C, 11·7; H, 2·0; Cl, 23·0; C_3H_6, liberated by aq. KCN, 13·4(5). $C_3H_6Cl_2Pt$ requires C_3H_6, 13·6%].

*Dipyridine*cyclo*propanedichloroplatinum*. "AnalaR" pyridine was condensed on to the first powder *in vacuo*, and the whole warmed to room temperature. No gas was evolved, but a white solid was formed, which dissolved in excess of pyridine to give a brown solution. Water was added and the *complex* was precipitated. It was filtered off, washed with water, and dried *in vacuo* (Found: Pt, 40·4; C, 33·6; H, 3·50; Cl, 15·0; C_3H_6, released by aq. KCN, 9·2. $C_{13}H_{16}N_2Cl_2Pt$ requires Pt, 41·9; C, 33·5; H, 3·44; Cl, 15·2; C_3H_6, 9·0%).

The infrared spectra were measured with a Grubb-Parsons double beam spectrometer. The finely powdered solid was suspended in hexachlorobutadiene for the region 2·5—4 μ and in "Nujol" for the region 4—14 μ.

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Department of Inorganic and Physical Chemistry,
University of Liverpool. [*Received, January 6th*, 1955.]

* The author thanks a referee for this suggestion.

Organosilicon Compounds. Part XIII. Co-ordination to Silicon.*

By C. Eaborn.

[Reprint Order No. 6017.]

With bases silicon tetrafluoride forms complexes in which silicon is 5- or 6-co-ordinated (Wilkins and Grant, *J.*, 1953, 927; Schumb and Cook, *J. Amer. Chem. Soc.*, 1953, **75**, 5133; Piper and Rochow, *ibid.*, 1954, **76**, 4318) but it has not been proved that co-ordination to silicon is involved in the complexes formed by chloro- and bromo-silanes (cf., *e.g.*, Harding, *J.*, 1887, **51**, 40; Trost, *Canad. J. Chem.*, 1951, **29**, 877, 1079; 1952, **30**, 835, 842; Burg, *J. Amer. Chem. Soc.*, 1954, **76**, 2674). Some, or all, of the complexes with amines may be quaternary ammonium salts, possibly solvated (cf. Emeléus and Miller, *J.*, 1939, 819; Piper and Rochow, *loc. cit.*), and co-ordination to halogen is as likely an explanation of the formation of 1 : 4 complexes between tetrachlorosilane and amines (Trost, *loc. cit.*) or tetrabromosilane and dioxan (Kennard and McCusker, *J. Amer. Chem. Soc.*, 1948, **70**, 1039) as Trost's suggestion that 4*s*, 3*d*, and 4*p* orbitals of silicon are involved in the co-ordination without disturbance of the sp^3 character of the Si–halogen bonds. There is no evidence that co-ordination to silicon occurs in silane derivatives other than halides, but it is often suggested as an initial rapid reaction step (*e.g.*, Gilman, Brook, and Miller, *ibid.*, 1953, **75**, 4531; Hauser and Hance, *ibid.*, 1951, **73**, 5846; Rochow, "The Chemistry of the Silicones," J. Wiley and Sons, New York, 2nd Edn. 1951, pp. 21—24), and Sujishi and Witz (*J. Amer. Chem. Soc.*, 1954, **76**, 4631) have attributed association in silyldimethylamine to intermolecular N→Si co-ordination. There is evidence against the existence of N→Si and O→Si co-ordination in organosilicon compounds, based on the strengths of organosilyl-alkylamines and carboxylic acids (Sommer and Rockett, *ibid.*, 1951, **73**, 5130), but in the aqueous media employed hydrogen-bonding to nitrogen and oxygen may break the co-ordination bonds.

We have now examined the ultraviolet absorption spectra of *p*-toluidine and pyridine in several organosilicon solvents. These conditions, in which fairly strong, relatively sterically-unhindered bases are dissolved in a large excess of the organosilanes, should favour N→Si co-ordination, and the consequent restriction on the lone pair of nitrogen should cause a large decrease in the absorption for *p*-toluidine and a marked increase in that for pyridine (cf. the effects of acids on the absorptions: Wohl, *Bull. Soc. chim. France*, 1939, **6**, 1312; Kumler and Strait, *J. Amer. Chem. Soc.*, 1943, **65**, 2349; Swain, Eisner, Woodward, and Brice, *ibid.*, 1949, **71**, 1341; Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26). In no case, however, does the absorption differ significantly from that in *n*-hexane, suggesting that co-ordination to silicon is not such a ready process as is often assumed; *e.g.*, it seems unlikely that such co-ordination causes association in silyldimethylamine. The existence of such co-ordination in short-lived reaction intermediates is not, of course, ruled out, but should not be accepted until there is experimental evidence in its favour (cf. Eaborn and Parker, *J.*, 1955, 126).

	p-Toluidine				Pyridine			
Solvent.	$\lambda_{max.}$ (mμ)		$\lambda_{min.}$ (mμ)		$\lambda_{max.}$ (mμ)		$\lambda_{min.}$ (mμ)	
n-Hexane...	293(1900)	237·5(9640)	267(580)	216(~350)	255·5(2010)	250·5(2080)	215(~220)	
$SiMe_2Et_2$ ...	293(1960)	237·5(9260)	267·5(550)	—*	not studied			
$SiEt_3F$	293(2070)	—*	—*	—*	255·5(1970)	—*	—*	
$C_6H_{11}·SiH_3$	294(1820)	238(9050)	268(570)	216(~350)	256(2020)	251(2090)	216(~200)	
$Si(OEt)_4$ ...	296(2070)	240(10,000)	268(600)	217(~350)	255·5(1960)	250·5(2090)	216(~250)	
$(SiMe_3)_2O$...	293(1810)	238(9250)	267·5(550)	215(~350)	255·5(1940)	250·5(2030)	215(~250)	

* Low transmittance of solvent prevented measurement.

The Table lists the extinction coefficients (in parentheses) at the main maxima and minima.

Experimental.—cyclo*Hexylsilane.* This, b. p. 118°, n_D^{20} 1·4471 (Found: C, 63·6; H, 12·6. Calc. for $C_6H_{14}Si$: C, 63·1; H, 12·4%), was prepared in 90% yield from trichlorocyclohexylsilane

* Part XII, *J.*, 1955, 1420.

and lithium aluminium hydride; Benkeser, Landesman, and Foster's directions for phenylsilane (*J. Amer. Chem. Soc.*, **1952**, **74**, 648) were followed except that the reaction mixture was boiled under reflux for 1 hr.

Spectra. A Unicam S.P.500 spectrophotometer was used. Emphasis was on relative rather than absolute accuracy in measurements of absorption intensities. The absorptions of the solutions did not change during some hours except for *p*-toluidine in tetraethoxysilane and triethylfluorosilane; for these the absorption increased, slowly in the former and more rapidly in the latter, with appearance of absorption at longer wavelengths. In the latter case the process was speeded by light and the solution became yellow. The reactions occurring were clearly not salt formation, which would lead to decrease in absorption, and they may have involved impurities in the solvent. The figures in the Table are for freshly prepared solutions.

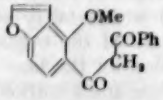
UNIVERSITY COLLEGE, LEICESTER. [*Received, January 7th*, 1955.]

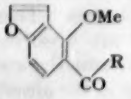
Chemistry of Pongamol. Part III. Synthesis.*

By S. K. MUKERJEE and T. R. SESHADRI.

[Reprint Order No. 6030.]

OF the possible methods for synthesis of pongamol (I) (Part II *), the condensation of 4-methoxybenzofuran-5-carbonyl chloride (II) with ethyl benzoylacetate in the presence of sodium ethoxide and of 5-acetyl-4-methoxybenzofuran (III) with ethyl benzoate did not proceed satisfactorily, but the simpler method in which the methyl ester (IV) was condensed with acetophenone proved convenient. The resulting pongamol (I) is best isolated and purified as the copper complex which is easily decomposed to yield pongamol. The synthetic and the natural product agree in melting point (mixed melting point), colour reaction with ferric chloride, and melting point of the copper complex, but differ in that

(I) 



(II; R = Cl)
(III; R = Me)
(IV; R = OMe)

in concentrated sulphuric acid the synthetic substance gives a permanent yellow colour whereas the natural sample, as originally recorded, yields a yellow colour becoming bright emerald-green in a few minutes. This seems to be due to an impurity in the natural product which is difficult to remove except by conversion into and decomposition of the copper complex. Pongamol recently obtained from *Tephrosia lanceolata* Grah. does not give the green colour with concentrated sulphuric acid but otherwise has all the properties of the sample obtained from *Pongamia glabra* (Rangaswami and Sastry, *Current Sci.*, **1955**, **24**, 13).

Experimental.—Methyl 4-methoxybenzofuran-5-carboxylate (Seshadri and Venkateswarlu, *Proc. Indian Acad. Sci.*, **1941**, **13**, *A*, 404) was prepared by refluxing a solution of the acid (1 g.) in dry acetone (50 c.c.) with methyl iodide (2 c.c.) and potassium hydrogen carbonate (5 g.) for 10 hr. It was obtained as a pale brown liquid and after being washed with aqueous sodium hydrogen carbonate and with water and dried was directly used for the next step.

The ester and acetophenone (1 c.c.) in dry ether (50 c.c.) were added to powdered sodamide (1 g.) covered with a layer of dry ether. The mixture was refluxed for 4 hr., left overnight, and then poured into excess of ice-cold dilute acetic acid, a brown semisolid mass separating. This was extracted with ether (6 × 25 c.c.), and the extract was repeatedly washed with aqueous sodium hydrogen carbonate (5%) and once with water. The bicarbonate extract on acidification yielded 4-methoxybenzofuran-5-carboxylic acid (0·4 g.), m. p. and mixed m. p. 148°. The ether solution was then concentrated to about 50 c.c. and vigorously shaken with saturated aqueous copper acetate. The ethereal layer became green and a yellowish-green crystalline precipitate gradually separated at the interface. After 24 hr. the precipitated complex was filtered off and washed first with a little ether and then with water. When dry, it crystallised

* Part II, *J.*, 1954, 1871.

from chloroform–ether as green rhombohedral tablets and prisms, m. p. 220—222° undepressed on admixture with the copper complex of natural pongamol.

The copper complex was suspended in 75% alcohol containing a little hydrochloric acid and warmed till a clear faintly greenish-yellow solution was obtained. Passage of hydrogen sulphide and filtration removed copper sulphide. The filtrate on concentration and cooling deposited pongamol as a brownish-yellow solid (0·2 g.). It crystallised from alcohol as pale brown rectangular tablets, melting alone or when mixed with the natural sample (from *P. glabra*) at 128—129°. It gave a blood-red colour with alcoholic ferric chloride and a yellow solution in concentrated sulphuric acid (Found: C, 73·5; H, 4·6. $C_{16}H_{14}O_4$ requires C, 73·5; H, 4·8%).

Department of Chemistry,
Delhi University, Delhi-8. [*Received, January 17th*, 1955.]

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p-*Nitrosoaniline.*

By J. Willenz.

[Reprint Order No. 6067.]

p-Nitrosoaniline was prepared by Fischer and Hepp (*Ber.*, 1887, **20**, 2474; see also Fischer and Schäffer, *Annalen*, 1895, **286**, 151) by heating "1 part of *p*-nitrosophenol with 5 parts of ammonium chloride, 10 parts of dry ammonium acetate and a little ammonium carbonate." Fischer (*Ber.*, 1888, **21**, 684) claimed a 50% yield. Attempts to repeat this preparation using pure reactants in glass apparatus were unsuccessful, but reaction in an iron crucible in the presence of ferric chloride as catalyst gave *p*-nitrosoaniline in up to 34% yield.

Experimental.—A finely ground mixture of *p*-nitrosophenol (16·25 g.), ammonium chloride (81·25 g.), ammonium acetate (162·5 g.), ammonium carbonate (17·5 g.), and ferric chloride (1·75 g.) was heated in an iron crucible on a steam-bath for 45 min. after which the mixture was homogeneous. The liquid product was poured into water at 0° to precipitate the crude *p*-nitrosoaniline. Dissolution in dilute sulphuric acid, filtration, basification with ammonia, and recrystallisation from benzene gave *p*-nitrosoaniline as bluish-black needles, (5·5 g., 34%), m. p. 173—174° (lit., 173—174°). The *monopicrate*, purified by precipitation from methanol with chloroform, decomposed at 166° (Found: C, 40·8; H, 2·8; N, 19·7. $C_{12}H_9O_8N_5$ requires C, 41·0; H, 2·6; N, 19·9%). The addition *compound* with 2:4-dinitrophenol had m. p. 116—117° (olive green crystals from ethanol) (Found: C, 46·7; H, 3·4; N, 18·2. $C_{18}H_{10}O_6N_4$ requires C, 47·0; H, 3·3; N, 18·3%).

Research Department, Imperial Chemical Industries Limited,
Billingham Division, Billingham, Co. Durham. [*Received, January 25th*, 1955.]

The Alkaloids of Picralima nitida, *Stapf, Th. and H. Durand. Part III.* A Note on Akuammicine and* pseudo*Akuammicine.*

By Sir Robert Robinson and A. F. Thomas.

[Reprint Order No. 6087.]

The separation of the petroleum-soluble bases of *Picralima* seeds has been described in Part II.* By means of its sparingly soluble hydrochloride (cf. Henry, *J.*, 1932, 2759), *pseudo*akuammicine is readily purified.

The formula, $C_{19}H_{20}O_2N_2$, proposed by Henry (*loc. cit.*) for akuammicine should now be replaced by $C_{20}H_{22}O_2N_2$ whereas *pseudo*akuammicine appears to be $C_{19}H_{20}O_2N_2$. The latter base has been available in very small amount; its infra-red absorption spectrum overlies that of akuammicine.

The ultra-violet spectra of akuammicine and echitamidine are characteristic and almost identical (Raymond-Hamet, *Compt. rend.*, 1951, **233**, 560); tabernosine (Janot, Goutarel,

* Part II, *J.*, 1954, 352.

and Le Men, *Bull. Soc. chim. France*, 1954, 707) and *pseudo*-akuammicine are from this point of view further members of the group. The indication is that the peculiar structure of the bands is due to an indole nucleus with additional conjugation. This is doubtless associated with the abnormally high rotatory powers of the bases, with the curious and possibly significant exception that *pseudo*akuammicine has a rotatory power within the more usual range.

The deep absorption band at 6·03 μ exhibited by akuammicine and *pseudo*akuammicine (Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89) was naturally interpreted as due to an amide-carbonyl group but if this is correct the group is quite stable towards lithium aluminium hydride. Further experiment is needed to resolve this apparent contradiction.

Added in Proof.—Under more vigorous conditions this reduction has now been effected by K. Aghoramurthy (personal communication).

Experimental.—Akuammicine hydrochloride crystallised slowly from water or aqueous alcohol as large glistening plates which on drying in a vacuum-desiccator broke into small leaflets, m. p. 143—146°. The leaflets contained $4H_2O$, half of which was removed on drying at 120°/0·01 mm. for 4 hr. The *dihydrate* had m. p. 171°, $[\alpha]_D^{21}$ −610° (*c*, 1·430 in EtOH) (Found: C, 61·0; H, 6·6; N, 7·1; Cl, 9·1. $C_{20}H_{22}O_2N_2,HCl,2H_2O$ requires C, 60·9; H, 6·9; N, 7·1; Cl, 8·8%).

The *base* crystallised from ethanol and a little water in colourless plates, m. p. 182°, $[\alpha]_D^{18}$ −745° (*c*, 0·994 in EtOH), pK_a 7·45 (Found: C, 74·6, 74·8; H, 7·1, 7·2; N, 8·6, 8·9. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9; N, 8·7%). The *perchlorate* separated from aqueous ethanol in lustrous needles of the dihydrate, m. p. 134—136° (Found: loss, 4·3. Found, in the dried sample: C, 55·0; H, 5·7; N, 6·9; Cl, 8·4. $C_{20}H_{22}O_2N_2,HClO_4,H_2O$ requires C, 54·5; H, 5·6; N, 6·4; Cl, 8·0%). The *hydriodide*, made from the hydrochloride and concentrated potassium iodide solution, crystallised from water in colourless, square plates of the dihydrate, m. p. 128° (Found: loss, 3·8. Found, in dried material: C, 51·4; H, 5·4; N, 6·0; I, 27·1. $C_{20}H_{22}O_2N_2,HI,H_2O$ requires C, 51·3; H, 5·4; N, 6·0; I, 27·1%).

Akuammicine develops a fine royal blue colour when a trace of dichromate is added to its solution in 80% sulphuric acid but it gives no characteristic reaction with ferric chloride in weak acid solution. It gives a bright green solution in concentrated nitric acid. The base does not couple with diazobenzenesulphonic acid under any conditions tried but, after reduction in boiling acetic acid with zinc dust and a trace of mercuric chloride, the product is convertible into a typical methyl-orange showing the usual indicator changes. This is probably due to a reduction either of an amide group (or C:N) or of an aromatic indole nucleus.

A solution of akuammicine in dilute acid becomes bright yellow on the addition of sodium nitrite.

The base was recovered unchanged after attempted reduction with lithium aluminium hydride in ether (2 hr.) or tetrahydrofuran (5 hr.). It was also stable to boiling methanolic potassium hydroxide (3%; 1½ hr.) and to boiling N-hydrochloric acid (2 hr.).

An attempt to acetylate the base was made as follows: akuammicine (200 mg.) was dissolved in dry pyridine (5 c.c.) and acetic anhydride (0·4 c.c.). Next day the mixture was diluted with water, and solid potassium hydrogen carbonate added. A precipitate was slowly formed, which had m. p. 178°, but on recrystallisation proved to be unchanged akuammicine. pseudo-*Akuammicine hydrochloride* crystallised from water as the monohydrate which can be completely dried only with great difficulty. After 5 hr. at 120°/0·01 mm. it had m. p. 217° (decomp. to red froth), $[\alpha]_D^{18}$ approx. 0 (*c*, 0·7 in 50% EtOH) [Found: loss 3·1. Found, in dried material: C, 64·8; H, 6·5; N, 8·3; Cl, 10·5, *C*-Me, 4·0. $C_{19}H_{20}O_2N_2$ (+2% of H_2O) requires C, 64·9; H, 6·3; N, 8·0; Cl, 10·1; *C*-Me, 4·3%].

The *base* forms glistening plates with a bluish lustre, m. p. 187° (decomp. to red froth), after recrystallisation from aqueous ethanol, $[\alpha]_D^{19}$ −83°, pK_a 7·47 (Found: C, 73·9; H, 6·6; N, 9·2. $C_{19}H_{20}O_2N_2$ requires C, 74·1; H, 6·6; N, 9·1%). The *perchlorate* separates as glistening needles from water or as leaflets from ethanol; it is very sparingly soluble in all solvents used, but with a 3-dm. tube, $[\alpha]_D^{21}$ approx. 0 (*c*, 0·2 in EtOH) was observed (Found: C, 55·7; H, 5·7; N, 6·6; Cl, 8·4. $C_{19}H_{20}O_2N_2,HClO_4,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 55·6; H, 5·6; N, 6·5; Cl, 8·2%).

The colour reactions of *pseudo*akuammicine are similar to those of akuammicine.

DYSON PERRINS LABORATORY, OXFORD. [*Received, February 1st*, 1955.]

The Resolution of 3-Methylpent-1-yn-3-ol.

By J. R. Hickman and J. Kenyon.

[Reprint Order No. 6097.]

The resolution of tertiary alcohols into their optical antipodes has presented considerable difficulty and it is only fairly recently (Doering and Zeiss, *J. Amer. Chem. Soc.*, 1950, **72**, 147; Zeiss, *J. Amer. Chem. Soc.*, 1951, **73**, 2391) that the practicability of such resolutions has become generally accepted. We now describe the preparation of optically active (+)-3-methylpent-1-yn-3-ol, CH:C·CMeEt·OH.

The alcohol was converted into its hydrogen phthalate, whose brucine salt was fractionally crystallised from acetone. The (+)-(hydrogen phthalate) was obtained from the brucine salt in the usual manner (see Table 1). From this ester was obtained the (+)-alcohol (see Table 2).

The present alcohol is the first tertiary acetylenic alcohol to be resolved and apparently presents the simplest and most straightforward resolution of any tertiary alcohol.

Table 1. *Specific rotatory powers of* (+)-1-*ethyl*-1-*methylprop*-2-*ynyl hydrogen phthalate in various solvents at room temperature* (*c*, 5·000).

Solvent	Temp.	$[\alpha]_{4358}$	$[\alpha]_{4800}$	$[\alpha]_{5086}$	$[\alpha]_{5461}$	$[\alpha]_{5780}$	$[\alpha]_{5893}$	$[\alpha]_{4358}/[\alpha]_{5461}$
Ethanol	19°	+95·6°	+64·8°	+58·8°	+48·0°	+44·0°	+39·0°	1·99
Ether	20	77·2	53·2	46·6	38·6	32·0	30·6	2·00
Acetone	18	72·6	49·6	45·8	26·4	32·8	29·2	2·00
Pyridine	19	64·2	47·2	40·4	33·0	28·0	27·0	1·95
Chloroform ...	18	60·4	41·2	39·6	30·0	27·2	24·2	2·01
Benzene	18	54·2	36·4	35·4	25·8	24·4	22·8	2·10

Table 2. *Observed rotatory powers of* (+)-3-*methylpent*-1-*yn*-3-*ol at* 21° (*l*, 1).

α_{4358}	α_{4800}	α_{5086}	α_{5461}	α_{5780}	α_{5893}	α_{6438}
+4·36°	+3·34°	+3·10°	+2·58°	+2·26°	+2·22°	+1·50°

(−)-1-Ethyl-1-methylprop-2-ynyl hydrogen phthalate was prepared by fractional crystallisation of partially lævorotatory hydrogen phthalate obtained from mixed intermediates of the corresponding brucine salt; the highest specific rotation obtained was $[\alpha]_{5893}^{18}$ −22·3° (*c*, 6·16 in benzene).

Experimental.—(±)-3-*Methylpent*-1-*yn*-3-*ol.* The alcohol was obtained by treating ethyl methyl ketone with ethynylmagnesium halide by the Grignard method, and had b. p. 121—122°/760 mm., m. p. 30—31°, n_D^{20} 1·4318, d_{20}^{20} 0·8721 (Found: C, 74·0; H, 10·3. Calc. for $C_6H_{10}O$: C, 73·5; H, 10·2%).

The alcohol (41 g.), phthalic anhydride (65 g.), and pyridine (65 g.) were heated at 90° for 2 hr., then treated with dilute hydrochloric acid and extracted with ether. The ether extract was washed with dilute hydrochloric acid, then with water, and dried. The crude hydrogen phthalate, after removal of the ether, was purified by dissolution in sodium carbonate solution and extraction with ether to remove unchanged alcohol; the aqueous solution was then acidified with dilute hydrochloric acid, and extracted with chloroform, and the extract dried. After removal of the chloroform, the inactive *hydrogen phthalate* (47 g., 45·5%) was obtained in cubes, m. p. 97—98° (Found, by titration with KOH: *M*, 244. $C_{14}H_{14}O_4$ requires *M*, 246).

Use of triethylamine in place of pyridine gave an 81% yield of much darker product.

(+)-1-*Ethyl*-1-*methylprop*-2-*ynyl hydrogen phthalate.* (±)-3-Methylpent-1-yn-3-yl hydrogen phthalate (47 g.) and anhydrous brucine (77 g.) were dissolved in the minimum quantity of boiling acetone and allowed to cool. Fine needles separated slowly, attaining optical purity after a total of six crystallisations. The final brucine salt had m. p. 148—149°. This was decomposed with dilute hydrochloric acid and extracted with ether, the extract washed and dried, and the ether removed, giving (+)-1-*ethyl*-1-*methylprop*-2-*ynyl hydrogen phthalate*, m. p. 112—113° (Found: *M*, 245).

(−)-1-*Ethyl*-1-*methylprop*-2-*ynyl hydrogen phthalate.* A mixture of the more soluble fractions produced in the resolution was decomposed into the partially pure lævorotatory hydrogen phthalate by means of dilute hydrochloric acid followed by ether-extraction and recovery of the ether

after washing and drying the extract. This material, $[\alpha]_{5893}^{20}$ −14·2° (*c*, 5·00; l, 1), was recrystallised four times from light petroleum and then had $[\alpha]_{5893}^{18}$ −22·3° (*c*, 5·00; l, 1), m. p. 112—113° (Found: *M*, 245).

(+)-3-*Methylpent*-1-*yn*-3-*ol*. The (+)-ester (18 g.) was steam-distilled with a slight excess of 10N-potassium hydroxide; the (+)-alcohol was then extracted from the distillate with ether, and the extract dried and fractionated. (+)-3-*Methylpent*-1-*yn*-3-*ol* (5 g.) thus obtained had b. p. 120—121°/760 mm., n_D^{19} 1·4317 (Found: C, 73·8; H, 10·5. $C_6H_{10}O$ requires C, 73·5; H, 10·2%).

(±)-1-*Ethyl*-1-*methylprop*-2-*ynyl* p-*nitrobenzoate*. The (±)-alcohol (1·0 g.), *p*-nitrobenzoyl chloride (2·0 g.), and pyridine (5·0 g.) at 90° rapidly gave this *ester*, plates (2·4 g.) (from aqueous alcohol), m. p. 68—69° (Found: C, 63·5; H, 5·4; N, 6·6. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

The (+)-*ester*, similarly prepared, had m. p. 75—76°, $[\alpha]_{5893}^{20}$ +12·8° (*l*, 0·5; *c*, 1·72 in EtOH).

(±)-1-*Ethyl*-1-*methylprop*-2-*ynyl hydrogen phthalate from its optical antipodes*. 0·200 g. each of pure (+)- and (−)-1-ethyl-1-methylprop-2-ynyl hydrogen phthalate were ground together and then had m. p. 97—99° and $[\alpha]_{5893}^{20}$ 0·00° (*l*, 0·5; *c*, 5·00 in C_6H_6).

Reduction of partially active (−)-3-*methylpent*-1-*yn*-3-*ol to the corresponding fully saturated inactive alcohol*. Partially lævorotatory 3-methylpent-1-yn-3-ol (3 g.) was reduced in ether solution with hydrogen (Pd–C) yielding 3-methylpentan-3-ol (2·2 g.), b. p. 122—123°, n_D^{20} 1·4183, d_4^{20} 0·8235 and having zero optical rotation.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, February 3rd*, 1955.]

2-*Alkoxypropenes*.

By H. P. CROCKER and R. H. HALL.

[Reprint Order No. 6114.]

DURING a recent study of the infrared absorption spectra of various αβ-unsaturated ethers (Philpotts and Ward, unpublished work), certain 2-alkoxypropenes were required. Some of these had been prepared previously (cf. Claisen, *Ber.*, 1898, **31**, 1019; Schmitt and Boord, *J. Amer. Chem. Soc.*, 1932, **54**, 751; Sherrill and Walter, *ibid.*, 1936, **58**, 743; Dolliver, Gresham, Kistiakowsky, Smith, and Vaughan, *ibid.*, 1938, **60**, 440; Shostakovskiĭ and Gracheva, *J. Gen. Chem. U.S.S.R.*, 1953, **23**, 1153); in the present instance they were conveniently obtained from the corresponding 2 : 2-dialkoxypropanes (cf. Claisen, *loc. cit.*). The physical constants of the methoxy- and *n*-propoxy-propene thus prepared, however, differed considerably from those recorded recently by Shostakovskiĭ and Gracheva (*loc. cit.*) and proof of structures was therefore required. Infrared absorption data showed that the unsaturated ethers were all very similar and elementary analyses, hydrogenation of the ethoxypropene to ethyl *iso*propyl ether, identical with an authentic specimen, and ozonolysis of the *iso*butoxypropene to formaldehyde and *iso*butyl acetate established that they were correctly formulated as 2-alkoxypropenes. Shostakovskiĭ and Gracheva's data (*loc. cit.*) may possibly refer to materials contaminated with alcohol: careful purification was necessary to afford spectroscopically pure specimens, free from the alcohol liberated in their preparation.

The 2 : 2-dialkoxypropanes required were accessible from acetone, either directly by reaction with orthoformic esters (cf. Claisen, *Ber.*, 1898, **31**, 1010) or by way of *iso*propenyl acetate (cf. Croxall, Glavis, and Neher, *J. Amer. Chem. Soc.*, 1948, **70**, 2805). The latter route was the one employed.

Experimental.—2 : 2-*Dialkoxypropanes*. These were prepared from *iso*propenyl acetate by the method of Croxall, Glavis, and Neher (*loc. cit.*), with the exception that yellow mercuric oxide was substituted for the red oxide. The yields and physical constants of the products are shown in Table 1. 2 : 2-*Di*-n-*propoxy*- and 2 : 2-*diisobutoxy*-*propane* are new compounds.

2-*Alkoxypropenes*. The following general method was used (cf. Claisen, 1898, **31**, 1019). The 2 : 2-dialkoxypropane (1 mol.) was added to a slurry of phosphoric oxide (1·1 mol.) and quinoline (1·1 mol.) (phosphoric oxide alone, or phosphoric acid, was unsatisfactory), and the mixture was heated in an oil-bath (140—180°) under a helices-packed column (2 × 30 cm.), fitted with a

TABLE 1. 2 : 2-*Dialkoxypropanes*, $Me_2C(OR)_2$.

R	Yield (%)	B. p.	n_D^{20}	R	Yield (%)	B. p.	n_D^{20}
Me	33	81°/756 mm.[a]	1·3778[a]	*n*-Pr[c]	44	91°/95 mm.	1·4026
Et	52[b]	113°/754 mm.[b]	1·3886[b]	*iso*-Bu[d] ...	32	65°/14 mm.	1·4068

[a] Claisen (*Ber.*, 1898, **31**, 1010) gives b. p. 83°; Killian, Hennion, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 1384) give b. p. 78—80°/747 mm., n_D^{20} 1·3746. [b] Croxall *et al.* (*ibid.*, 1948, **70**, 2805) give a yield of 55%, b. p. 113—113·5°, n_D^{20} 1·3891. [c] Found: C, 67·45; H, 12·7. $C_9H_{20}O_2$ requires C, 67·45; H, 12·6%. [d] Found: C, 70·55; H, 12·7. $C_{11}H_{24}O_2$ requires C, 70·15; H, 12·85%.

variable take-off still-head. Crude product was taken off at the lowest head-temperature attainable. 2 : 2-Di*iso*butoxypropane was readily de-alcoholated; the dimethoxy-compound required more prolonged heating (36 hr.). The yield of crude product was about 10% in excess of theory.

In the case of 2-ethoxypropene the infrared spectrum of the crude product showed that about 20% of ethyl alcohol was present. This could not be removed completely by fractionation, as an azeotrope, b. p. 58°/747 mm., n_D^{20} 1·3871, containing 10% of alcohol, was formed.

The crude ethers were purified by repeated washing with successive small amounts of water, dried (KOH), and fractionated from unchanged ketal. With the more water-soluble methyl ether flakes of sodium were added and when no more effervescence occurred the liquid was fractionated.

The yields and properties of the ethers are summarised in Table 2. 2-iso*Butoxypropene* is a new compound.

TABLE 2. 2-*Alkoxypropenes*, $CH_2{:}CMe{\cdot}OR$.

R	Yield (%)[a]	B. p.	n_D^{20}	Formula	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
Me	22	33·5°/750 mm.[b]	1·3827[b]	C_4H_8O	66·4[c]	11·5[c]	66·65	11·2
Et	26	61°/747 mm.[d]	1·3918[d]	$C_5H_{10}O$	69·75	11·4	69·75	11·7
n-Pr	44	88·5°/756 mm.[e]	1·4017[e]	$C_6H_{12}O$	72·0	12·1	72·0	12·1
iso-Bu	53	104·5°/752 mm.	1·4043	$C_7H_{14}O$	74·15	12·2	73·65	12·35

[a] Spectroscopically and analytically pure material. [b] Shostakovskiĭ and Gracheva (*J. Gen. Chem. U.S.S.R.*, 1953, **23**, 1153) give b. p. 28°/759 mm., n_D^{20} 1·3751; Claisen (*Ber.*, 1898, **31**, 1019) gives b. p. 38°. [c] Analysis difficult owing to volatile nature of compound; figures quoted are mean of five determinations. Shostakovskiĭ and Gracheva (*loc. cit.*) analysed a polymer of the ether. [d] *Idem* (*loc. cit.*) give b. p. 63—64°/749 mm., n_D^{20} 1·3913; Sherrill and Walter (*J. Amer. Chem. Soc.*, 1936, **58**, 743) give b. p. 61·2—61·8°/760 mm., n_D^{20} 1·3913; Schmitt and Boord (*ibid.*, 1952, **54**, 751) give b. p. 61—63°/748 mm. n_D^{20} 1·3915; Dolliver *et al.* (*ibid.*, 1938, **60**, 440) give b. p. 61·90°/765 mm., n_D^{20} 1·3927. [e] Shostakovskiĭ and Gracheva (*loc. cit.*) give b. p. 78·5°/756 mm., n_D^{20} 1·3990.

Hydrogenation of 2-*ethoxypropene*. The ether (7·65 g.) in toluene (50 ml.) was shaken in hydrogen in the presence of Adams catalyst (0·1 g.) (1·15 mol. of hydrogen absorbed). Infrared examination of the crude product (5·2 g.), b. p. 53—54°/752 mm., n_D^{20} 1·3632—1·3702, recovered from the solvent by fractionation, showed that it consisted of ethyl *iso*propyl ether, together with traces of compounds containing hydroxyl and carbonyl groups. It was therefore washed with water (5 × 10 ml.), dried (Na), and distilled, giving a product, n_D^{20} 1·3638, the infrared spectrum of which was virtually indistinguishable from that of a synthetic sample of ethyl *iso*propyl ether of b. p. 54·5°/756 mm., n_D^{20} 1·3632 (cf. Bennett and Philip, *J.*, 1928, 1931).

Ozonolysis of 2-iso*butoxypropene*. Ozonised oxygen was passed at room temperature through a solution of the ether (15 g.) in carbon tetrachloride (250 ml.) until the exit gases contained ozone. The solution was concentrated under reduced pressure and the ice-cold residue was agitated with a stream of nitrogen whilst a slurry of zinc dust (20 g.) in water (80 ml.) was added. The resultant mixture was kept overnight at room temperature and the zinc dust then filtered off and washed with ether. The aqueous filtrate, after extraction with ether (4 × 20 ml.), yielded the dimedone derivative of formaldehyde, m. p. and mixed m. p. 189°. The combined ether washings and extracts were dried (Na_2SO_4) and evaporated to give *iso*butyl acetate (7·5 g.) (Found: equiv., 115. Calc. for $C_6H_{12}O_2$: equiv., 116), from which *p*-bromophenacyl acetate, m. p. and mixed m. p. 85°, was prepared.

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THE DISTILLERS CO., LTD., RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY.

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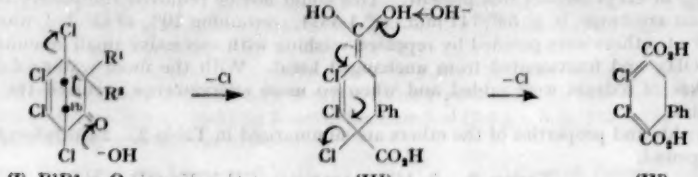
Hydration of a Bridged α-Diketone.

By R. H. Burnell and W. I. Taylor.

[Reprint Order No. 6123.]

Previously we postulated (*J.*, 1954, 3636) that the base-catalysed rearrangement of 1 : 2 : 3 : 4-tetrachloro-5 : 6-dioxo-7-phenyl*bicyclo*[2 : 2 : 2]oct-2-ene (I) proceeded *via* a keten intermediate to give the dicarboxylic acid (IV). Although the substance (I) has an absorption maximum (λ 446 mμ, ε 175) typical of an α-diketone (cf. Leonard and Mader, *J. Amer. Chem. Soc.*, 1950, **72**, 5388) in dry benzene, yet in aqueous or aqueous-ethanolic solution this band was replaced by a maximum at 310 mμ (ε 174) indicative of an isolated ketone group (cf. Cookson, *J.*, 1954, 282). This is best interpreted as due to hydration of one of



(I) $R^1R^2 = O$
(II) $R^1 = R^2 = OH$

(III) (IV)

the keto-groups to form the structure (II); hence the monohydrate isolated by Horner and Merz (*Annalen*, 1950, **570**, 89) is a true compound. The rearrangement of the compound (I) in alkaline solution therefore takes place according to the annexed scheme, where the intermediate (III) satisfactorily replaces the high-energy keten proposed earlier. Thus the first step in this reaction is a special case of base-catalysed fission of the type:

$$R^1{\cdot}CO{\cdot}CR^2R^3{\cdot}CR^4R^5X + OH^- \longrightarrow R^1{\cdot}CO_2H + CR^2R^3{:}CR^4R^5 + X^-$$

For a summary of examples of this reaction see Eschenmoser and Frey (*Helv. Chim. Acta*, 1952, **35**, 1660).

The carbonyl stretching frequencies of the diketone (I) at 1770 and 1750 cm.$^{-1}$ and of the " hydrate " (II) at 1770 cm.$^{-1}$ are very high and are thought to be a measure of the rigidity of the system and the effect of the carbon–chlorine dipoles on the neighbouring carbonyl groups. Although it is well known that 1 : 2 : 3-triketones are easily hydrated, α-diketones, *e.g.*, camphorquinone, $\lambda_{max.}$ 474 mμ (ε 38·4 in 95% ethanol; ε 36·1 in light petroleum), do not become hydrated. In our case there must be an increase in stability of the molecule through hydration or, in other words, some relief in the steric strain in going from structure (I) to structure (II).

The infrared spectra were measured in potassium bromide discs by Mr. W. Fulmor and staff, American Cyanamid Co., Lederle Laboratories Division. We are indebted to the National Research Council of Canada for a grant.

University of New Brunswick, Canada. [*Received, February 11th*, 1955.]

α- and β-Methyl L-*Fucofuranosides.*

By Winifred M. Watkins.

[Reprint Order No. 6155.]

For studies on the enzymic degradation of the blood-group mucoids, the methyl L-fucosides were required as possible synthetic substrates. α- and β-Methyl L-fucopyranosides have been obtained crystalline (Hockett, Phelps, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1658) but the furanosides have not been described. Augestad, Berner, and Weigner (*Chem. and Ind.*, 1953, 376) and Augestad and Berner (*Acta Chem.*

Scand., 1954, **8**, 251) reported the preparation of new crystalline methylfuranosides of galactose, arabinose, and xylose and the separation of the isomeric glycosides on a column of powdered cellulose. They found that a boiling methanolic solution containing very little hydrogen chloride gave the best yield of the furanosides and this method has now been employed in the preparation of the methyl L-fucofuranosides. By separation on a cellulose column α-methyl L-fucofuranoside was isolated in a crystalline form and β-methyl L-fucofuranoside as a syrup.

Experimental.—L-Fucose (1 g.) was heated in methanol (50 ml.) containing 0·012% of hydrogen chloride under reflux until it no longer reduced Fehling's solution (6 hr.). Hydrogen chloride was removed with lead carbonate, and the solution evaporated to a syrup which was examined by paper chromatography with ethyl methyl ketone saturated with water as solvent. The papers were sprayed with sodium metaperiodate followed by Schiff's decolorised magenta reagent (Buchanan, Dekker, and Long, *J.*, 1950, 3162), and the syrup was shown to contain four substances all of which were faster-running than L-fucose. One had an R_F value identical with that of α-methyl L-fucopyranoside (Fischer, *Ber.*, 1895, **28**, 1160); these spots were greenish-purple in colour. Two of the components, which ran more quickly than the α-pyranoside and by analogy with the methyl galactosides described by Augestad and Berner (*loc. cit.*) were thought to be the α- and β-furanoside, gave bright blue spots with Schiff's spray. The fourth spot, which moved more slowly than the α-pyranoside, gave a purplish-blue spot.

A concentrated solution of the syrup in ethyl methyl ketone was placed at the top of a column (50 × 2 cm.) of powdered cellulose. Ethyl methyl ketone saturated with water was used as the mobile phase and the effluent, collected automatically in 3-ml. fractions, left the column at the rate of 36 ml. per hour. One drop of each fraction was placed on filter paper and sprayed with periodate and Schiff's reagent. The spots developed a blue colour at tube no. 35 and a colour was detected continuously up to tube no. 150. The fractions were pooled in pairs, dried (Na_2SO_4), and examined in the polarimeter. The material eluted first (fractions 34—54) showed a positive rotation and the values obtained gave a symmetrical peak. The succeeding fractions gave a negative rotation but did not show a well-defined peak. Chromatograms were then run on the contents of every other tube and it was found that tube nos. 35—48 contained a single component and that the second-fastest-running component was present alone in tubes 55—64. The intermediate tubes contained a mixture of the two materials. Fractions 75—78 gave crystalline α-methyl L-fucopyranoside, m. p. 153°, $[\alpha]_D$ −196° (*c*, 1% in H_2O), and fractions 120—150 crystalline β-methyl L-fucopyranoside, m. p. 121°, $[\alpha]_D$ +10° (*c*, 1% in H_2O).

β-Methyl L-fucofuranoside. Fractions 35—48 were pooled and evaporated to a syrup which was redissolved in dry ethyl acetate, heated with charcoal, filtered, and concentrated. The clear syrup obtained had $[\alpha]_D$ +113 (*c*, 2% in H_2O). A paper chromatogram showed that only one sugar derivative was present, and hydrolysis with N-hydrochloric acid for 24 hr. at 100° followed by estimation of reducing sugar by Nelson's method (*J. Biol. Chem.*, 1944, **153**, 375) indicated that the syrup was 99% methyl glycoside. The syrup has not crystallised, however, after six months at −18°. A 0·2% solution of the material was 50% hydrolysed in 100 hr. by N-hydrochloric acid at room temperature. β-Methyl L-fucopyranoside was not detectably hydrolysed under the same conditions.

Crystalline α-methyl L-fucofuranoside. Fractions 55—64 were pooled and on evaporation the syrup crystallised spontaneously. Chromatographic examination showed that only one sugar derivative was present. A 0·2% solution of the material in N-hydrochloric acid was 50% hydrolysed after 24 hr. at room temperature, whereas a 0·2% solution of α-methyl L-fucopyranoside in the same acid did not become reducing after 128 hr. at room temperature. After recrystallisation from dry ethyl acetate the *α-methyl L-fucofuranoside* had m. p. 125—126°, $[\alpha]_D$ −108° (*c*, 2% in H_2O) (Found: C, 47·4; H, 8·1; OMe, 17·6. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9; OMe, 17·4%).

This work was carried out during the tenure of a Beit Memorial Research fellowship.

LISTER INSTITUTE OF PREVENTIVE MEDICINE, LONDON, S.W.1. [*Received, February 8th*, 1955.]

A Wolff–Kishner Reduction Procedure for Sterically Hindered Carbonyl Groups.

By D. H. R. Barton, D. A. J. Ives, and B. R. Thomas.

[Reprint Order No. 6166.]

The reduction of sterically hindered carbonyl groups by either the Clemmensen or the Wolff–Kishner procedure is not easily effected. In his classical work on adrenocortical steroids Reichstein (see Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161) removed the very hindered ketone group of an 11-oxo-steroid using modified Clemmensen conditions (heavily amalgamated zinc). An alternative Wolff–Kishner procedure for the reduction of 11-oxo-steroids was reported by Moffett and Hunter (*J. Amer. Chem. Soc.*, 1951, **73**, 1973). This employs sodium methoxide in methanol at 200° with "anhydrous" hydrazine. Neither of these methods of reduction is suited for relatively large-scale work. We have found that, whilst the Wolff–Kishner procedure of Huang-Minlon (*ibid.*, 1949, **71**, 3301), as indeed he states, does not reduce sterically hindered carbonyl groups, the simple precaution of using *completely* anhydrous hydrazine and keeping all water, so far as possible, out of the reaction system improves its reducing power remarkably. This reduction procedure was first developed by us for the preparation of fairly large quantities of lanostanol from 7 : 11-dioxolanostanyl acetate (see Barton, Ives, and Thomas, *J.*, 1954, 903). It has been used successfully in the reduction of 11-oxo-steroids (Djerassi and Thomas, *Chem. and Ind.*, 1954, 1228) and of hindered triterpenoid ketones (Beaton, Spring, Stevenson, and Stewart, *ibid.*, 1955, **35**; personal communication from Professor Carl Djerassi). Its application in the reduction of certain hindered 15-oxo-steroids has also been mentioned (Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852; *Chem. and Ind.*, 1954, 605).

Experimental.—Reduction of 7 : 11-*dioxolanostanyl acetate.* Sodium (10 g.) in diethylene glycol (500 ml.; redistilled) was heated to 180° (all temperatures measured with thermometer in liquid) and *completely anhydrous* hydrazine [prepared by refluxing hydrazine hydrate (60 ml.; 100%) over sodium hydroxide pellets (60 g.) for 3 hr.] was distilled in until the mixture refluxed freely at 180°. All operations were carried out in all-glass apparatus carefully protected from atmospheric moisture. The solution was cooled, 7 : 11-dioxolanostanyl acetate (Dorée, McGhie, and Kurzer, *J.*, 1948, 988) (50 g.) added quickly, and the solution refluxed overnight. The temperature was then raised to 210° by distilling some of the hydrazine back into the hydrazine generator and the solution refluxed at this temperature for 24 hr. Dilution with water and benzene-extraction gave, after reacetylation in the usual way and crystallisation from chloroform–methanol, lanostanyl acetate (Voser, Mantavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165) (32 g., 69%), m. p. 149—150°, resolidifies and remelts at 156—157°, $[\alpha]_D$ +40° (*c*, 1·67 in $CHCl_3$).

Two of us (D. A. J. I. and B. R. T.) are indebted to the International Wool Secretariat for (respectively) Predoctorate and Postdoctorate Research Fellowships.

Birkbeck College, London, W.C.1. [*Received, February 22nd*, 1955.]

Some Newer Aspects of the Organic Chemistry of Nitrogen.

HUGO MÜLLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON THURSDAY, DECEMBER 16TH, 1954.

By G. R. CLEMO.

I SHOULD like to introduce this Lecture with a few points from H. E. Armstrong's characteristic obituary notice (1917) of the man who endowed it. Hugo Müller worked with Wöhler (1852) and was an assistant to Liebig in Munich when he was invited by Hofmann in 1853 to become private assistant to Warren De la Rue. Later, Hugo Müller became a partner in the latter's firm and as "the prototype of the modern industrial chemist . . . he ultimately became a very wealthy man." He was President of the Chemical Society in 1885—1886 and retired from business in 1902 and was thereafter happy in his garden and "particularly in the last dozen years of his life in the laboratory seeking to contribute to the solution of the problems which Nature ever held before him." Armstrong states that he died of a broken heart in 1917 and his widow and daughter made handsome gifts to the Society. This Lecture is given every 3 years and alternates between a topic linking chemistry with mineralogy and one linking chemistry with botany. My subject will, I hope, fulfill the latter requirement and allow us to take a glance at a few of the problems which Nature holds before us.

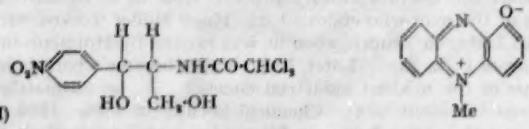
The three basic processes in Nature are photosynthesis, respiration, and nitrogen fixation; and as the latter is the basis of all natural organic nitrogen compounds—the amino-acids, the pre-eminently important proteins, the alkaloids, etc.—it is fitting to start by summarising the present knowledge of nitrogen fixation.

The sources of nitrogen for plant syntheses are free nitrogen, ammonium salts, and nitrates. Some years ago a crop analysis over a vast land area of the U.S.A. showed that two-thirds of all organic plant nitrogen was fixed by bacteria, one-quarter came from rainfall, and only one-twelfth from added fertilizers. It is stated, however, that 90% of all plant synthesis occurs at or near the surface of the seas, and no claim has been made for nitrogen fixation in this case. The soil has a colossal microbiological population (estimated at 5×10^9 bacteria per g. !) and of these the *Rhizobium* root bacteria of nodules and the two kinds of *Azotobacter* in the soil are responsible for nitrogen fixation by enzymes. That a definite relation exists between photosynthesis and nitrogen fixation appears to have been first established when Kamen showed in 1949 that illumination increased the assimilation of nitrogen by the photosynthetic bacterium *R. rubrum*. Wall and his co-workers later showed ammonia to be the key intermediate in the nitrogen fixation of the three types of photosynthetic bacteria, *Chromatium*, *Chlorobacterium*, and *R. rubrum*. The mechanism whereby nitrogen is thus enzymically converted into ammonia is, however, chemically still obscure. The dissociation energy of molecular nitrogen is so large (170 kcal./mole) that fission into atoms seems unlikely and possibly both nitrogen and oxygen molecules are brought into reaction by enzyme catalysts through the aid of some of the metals cobalt, iron, nickel, vanadium and particularly manganese and molybdenum. Virtanen has been the chief worker on the mode of action of *Rhizobium* root-nodule bacteria and, having detected oxime-nitrogen in some cases, suggested hydroxylamine as an intermediate ($N_2 \longrightarrow N_2O \longrightarrow H_2N_2O_2 \longrightarrow NH_2{\cdot}OH$); but this hypothesis has not been accepted and Virtanen himself stated at the 6th International Congress of Microbiology in 1953 that whilst there is evidence of the participation of hydroxylamine in amino-acid formation, ammonia appears to be the central compound in their synthesis. Newton, Wilson, and Burris (*J. Biol. Chem.*, 1953, **204**, 445), using ^{15}N, claim to have demonstrated the production of ammonia by *Azotobacter* by finding a high ^{15}N level in the glutamic acid; the chemistry invoked was: conversion of nitrogen into ammonia by various unknown steps involving energy; utilisation of ammonia for synthesis of glutamic acid by reductive amination; and formation of other amino-acids by transamination.

Burk (1934) claimed, however, that either ammonia or nitrate ion inhibited nitrogen fixation by *Azotobacter*.

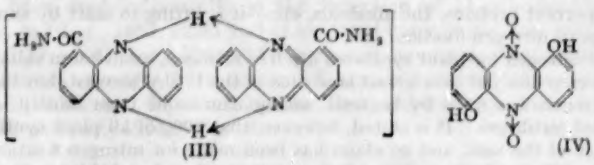
Recently, Virtanen, using peas, provided evidence that all effective nitrogen-fixing nodules contained a red hæmoglobin pigment, leghæmoglobin, with a molecular weight of about 34,000, whose function is to store and transfer oxygen and in whose absence nitrogen fixation does not occur. Virtanen claims that the nodules excrete amino-dicarboxylic acids to the cytoplasm which then effect transamination of α-keto-acids (*e.g.*, the fundamental L-aspartic

acid could form α-alanine from pyruvic acid, and either α- or β-alanine by simple loss of carbon dioxide). In spite of the large amount of work on amino-acids by those mentioned and by others, such as Chibnall, the mechanism of the fundamental fixation of nitrogen by *Rhizobium* and particularly by *Azotobacter* remains unexplained. As for the utilisation of nitrates, so important for marine synthesis, it is claimed that nitrate is first reduced to ammonia, and although Quastel has done much valuable work on the reaction its mechanism is also unknown. In this connection the striking discovery in 1948 of the first natural product with a nitro-group present in the soil, namely, chloromycetin (I) (note the C_6C_3 unit so common in natural products),



(I) (II)

doubtless has a significance apart from the fact that it is the best-known remedy for the dirt-borne disease typhoid fever! Our lack of precise knowledge as to how nitrogen, free or fixed, is utilised in nitrogen fixation is in marked contrast with the striking story of the actual transmutation of nitrogen into carbon ($^{14}_{7}N + n \longrightarrow {}^{14}_{6}C + p$); and, since the isotopes, particularly of carbon, hydrogen, oxygen, nitrogen, and sulphur, are confidently expected to help greatly in the elucidation of biological processes, we will now take note of some of the help thus given already. First, however, a brief account of my own limited incursion into the field of bacterial nitrogen fixation.



(III) (IV)

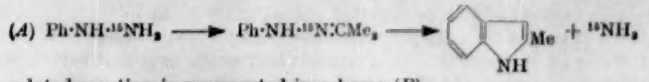
The phenazine ring systems in pyocyanine (II), chlororaphin (III), and chromo-iodinum (IV) are produced by bacteria, the first by the common *B. pyocyaneus* of pus. This usually needs organic nitrogen for its growth and pigmentation, but thanks to the kindness of Professor Dunlop of the Department of Bacteriology of King's College (Newcastle-on-Tyne) and the skill of Mr. T. K. Miller, B.Sc., of that Department a strain was found, after over 100 varieties from hospital patients had been tested, which grew and became pigmented on a medium containing the "AnalaR" reagents, magnesium sulphate, potassium dihydrogen phosphate, sodium acetate and citrate, and ferrous sulphate (the last is not essential but it inhibits the concurrent formation of a yellow pigment), to which combined inorganic nitrogen was added. If hydroxylamine was added no growth occurred, but with ammonium nitrate good growth and pigmentation took place whilst with potassium nitrate colour production was poor. In order to determine whether one or both of the nitrogen atoms in the phenazine ring of pyocyanine came from the ammonium or nitrate ions, $^{15}NH_4NO_3$ (32·5% enriched) was added to the medium. The resulting blue pigment was isolated by extraction with chloroform and recrystallised from water to give lovely deep blue needles, m. p. 133°. Analyses for carbon, hydrogen, and nitrogen were, however, no more successful than with the earlier workers, but the ultraviolet spectrum and melting point leave no doubt that it was pure pyocyanine. My best thanks are also offered to Mr. P. Kennedy for assistance with the preparative work involved and especially to Mr. P. Kelly, B.Sc., who in the absence of published data on the mass-spectrographic determination of ^{15}N in small samples had to devise the technique for its assay. In view of the cost * of the $^{15}NH_4NO_3$ used, only a few mg. of the pigment were obtained in each experiment, but it was found that admixture with unlabelled pyocyanine enabled reproducible ^{15}N figures to be obtained. The enrichment values thus found for the pyocyanine were 29·4, 28·9, and 32·7 ± 1%, thus proving that almost all the phenazine nitrogen came from the ammonium and *not* the nitrate ion. The poor result from potassium nitrate suggests that the bacteria cannot effectively reduce the nitrate ion to ammonia, and that the nitrate is not

* The only suitable isotope of nitrogen is the stable ^{15}N available as $^{15}NH_4NO_3$ (£90 approx. for 1 g. of ^{15}N) and as phthalimide. Although the natural abundance of ^{15}N is 0·38%, the price is an indication of the elaborate fractionation involved in the enrichment up to even 30%.

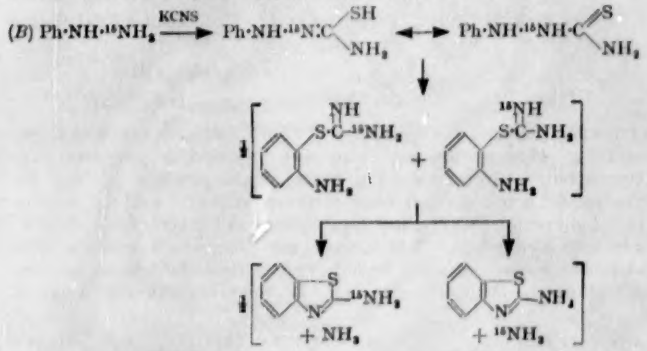
really needed for the bacterial utilisation of the ammonia is shown by the good result obtained by using ammonium chloride as the sole source of nitrogen present.

The following are some of the main uses of ^{15}N with a few examples, from the many, of the application of ^{14}C to problems in chemistry. In view of the fact that the main application of organic chemistry in recent years has been to biochemical problems it is not surprising that the chief use of the isotopes has been to them. A striking result of this application has been to reveal the surprising dynamic condition of many molecules. Few chemists, I think, expected to find all the hydrogen atoms of phenol so easily replaceable by deuterium and Schoenheimer's work has proved the rapid dynamic condition of even such very complicated molecules as make up the protein content of animals. Thus, using labelled amino-acids, he showed the rate of protein synthesis in the rat to be 11 g. of nitrogen per kg. body weight per day and when [^{15}N]leucine or [^{15}N]glycine was fed the ^{15}N appeared in almost all the amino-acids.

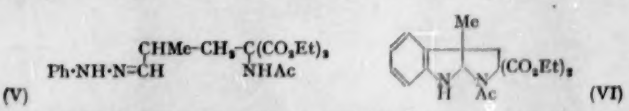
Of purely chemical interest was the following use of ^{15}N to confirm Robinson's views of the mechanism of the Fischer indole reaction, as set out in the annexed formulæ (*A*).



A related reaction is represented in scheme (*B*).

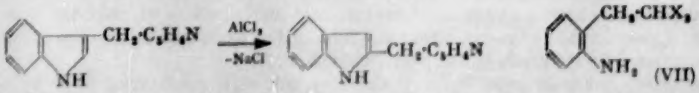


An interesting recent application of the Fischer indole reaction is by H. Kissmans, Ark, and B. Witkop (*Experientia*, **1952**, **8**, 36) in which the compound (V) yields the ring systems of physostigmine (VI). Recently, certain 3-substituted indoles, *e.g.*, skatole and 3-2′-pyridyl-



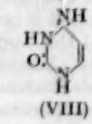
(V) (VI)

methylindole, have been shown to give the 2-substituted isomers when heated with aluminium chloride and sodium chloride (Clemo and Seaton, *J.*, 1954, 2582). This change does not take place when the indole-NH is acetylated.



The simple di- and tri-meric indoles have excited interest for many years and in a recent study (G. F. Smith, *Chem. and Ind.*, **1954**, 1451) good reasons are given for structure (VII; X = 3-indolyl) for the trimer. The linear structure of the azides was confirmed by using ^{15}N (Clusius and Weisser, *Helv. Chim. Acta*, 1952, **35**, 1958). ^{15}N has been used successfully in the purine field. It is of interest to note that whilst this ring system is of the greatest importance the parent purine itself has only recently been found in Nature in a mushroom (Löfgrin and Lüning, *Acta Chem. Scand.*, 1953, **7**, 225). The easy preparation of ^{15}N-labelled urea and guanidine has led to the syntheses of cytosine (VIII), uric acid (IX), xanthine (X), hypoxanthine (XI), and guanine (XII), all 1 : 3-labelled with ^{15}N; and use of ^{13}C, ^{14}C, and ^{15}N in

combination in uric acid has led to the elucidation of both its biosynthesis and its degradation. In the latter case the surprising result has emerged that in the oxidative degradation the five-membered ring of allantoin (XIII) comes equally from the five- and six-membered rings of uric acid.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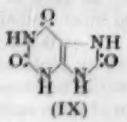
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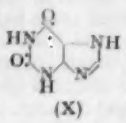
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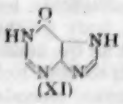
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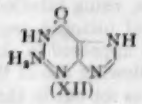
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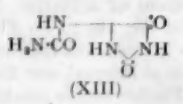
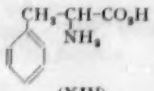

(XIII)

From the large number of isotopic studies already carried out in the biochemical field it is possible to glance at only a few. If phenylalanine (XIV) is given in food, even in the presence of sufficient tyrosine, it is converted into tyrosine (XV) in the liver and is then decarboxylated by kidney tissues to tyramine, the postulated precursor of adrenaline (XVI):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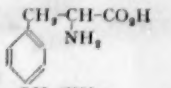
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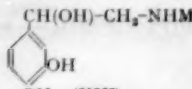
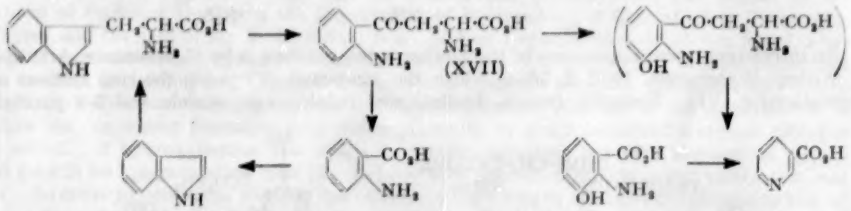

(XVI)

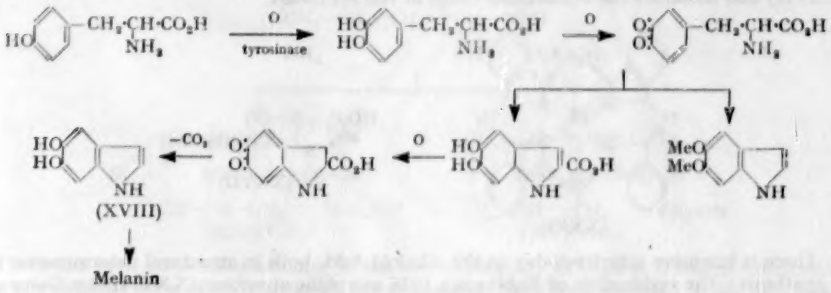
Very striking transformations of tryptophan *via* anthranilic acid into nicotinic acid have also been demonstrated. Thus several organisms such as *Claviceps purpurea* (ergot) can convert indole into tryptophan by interaction with serine in the presence of the coenzyme pyridoxal phosphate, the indole being derived from anthranilic acid. Certain moulds easily convert tryptophan into kynurenine (XVII), and *Neurospora* can convert the latter *via* anthranilic acid and indole back into tryptophan. 3-Hydroxykynurenine, which occurs in Nature, can replace nicotinic acid in the growth of some moulds and is thus claimed as an intermediate in the conversion of tryptophan into nicotinic acid. In this connection 3 : 4-fission of 3-hydroxy-


(XVII)

anthranilic acid has been claimed, and the recent work of Wass (*Z. Naturforsch.*, **1954**, **9**b, 740) on the enzymic oxidation of 3-hydroxyanthranilic acid strongly supports it. Leifer, Langham, Nye, and Mitchell (*J. Biol. Chem.*, **1950**, **184**, 589), growing *Neurospora* with $^{15}NH_4Cl$, furthermore claimed a diamino-compound as an intermediate in the conversion of 3-hydroxyanthranilic acid into nicotinic acid since half of the nicotinic acid nitrogen was ^{15}N, but the interpretation of this work appears to have been questioned. The earlier work on this important but involved cycle was discussed by Dalgliesh (*Quart. Rev.*, **1951**, **5**, 227).

The use of ^{14}C has shed some light on the still unknown mechanism whereby tyrosine is converted into the black melanin pigment. Although such pigments are widespread in hair, some skins, and potatoes, and in certain pathological conditions, they are probably not all identical. Raper (*Biochem. J.*, **1927**, **21**, 87) showed that tyrosinase converted tyrosine into melanin with the uptake of 5·2 oxygen atoms per molecule and the loss of carbon dioxide and when he isolated 5 : 6-dimethoxyindole by methylation at an intermediate stage he postulated 5 : 6-dihydroxyindole (XVIII) as the intermediate in melanin formation (see annexed scheme). This point was first proved rigidly by Robertson's synthesis of this dihydroxyindole which in alkaline solution rapidly changed to melanin (*J.*, **1948**, 223). In spite of this proof and of other work of Robertson, Burton, and Harley-Mason in this country and of Mason in the U.S.A., little

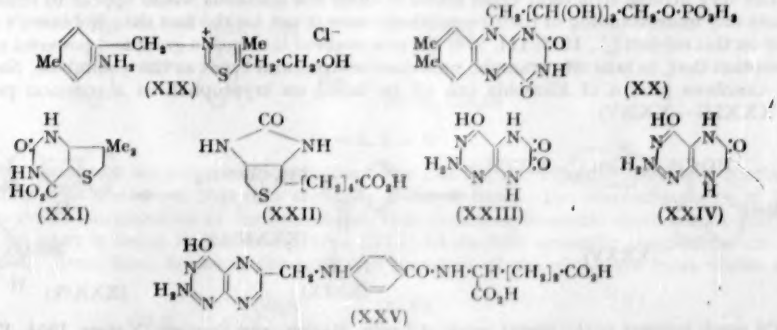
is known today of the stages in the conversion of the indole into melanin. In Raper's scheme it was assumed that the carbon dioxide evolved came from the carboxyl group of the tyrosine but when this group was labelled as $^{14}CO_2H$, the Lecturer (with Drs. Swan and Duxbury) found



that half of the carbon dioxide evolved came from some other carbon atom. It had been shown earlier that 3 : 4-dihydroxyphenylethylamine easily formed a melanin and when we labelled its α- and its β-carbon atom severally, the carbon dioxide evolved was found to be nearly inactive and in fact 96% of it came from the carbon of the benzene ring. Robertson has shown however that in the conversion of 3 : 4-dihydroxyindole into melanin (non-enzymically) 0·46 mol. of hydrogen peroxide is evolved (*J.*, **1954**, 1947); and we showed that if catalase is present to decompose the hydrogen peroxide the evolution of carbon dioxide is much reduced. Thus in the absence of catalase we found that one carbon atom from the ring of each two molecules of the indole was evolved as carbon dioxide but only one atom from four molecules of the indole was so evolved when catalase was present. Fission of the catechol ring has been demonstrated (Clemo and Duxbury, *Chem. and Ind.*, 1953, 1364) and it seems possible that this ring in the dihydroxyindole may split—although, as mentioned above for the tryptophan cycle the pyrrole ring can also be opened under biological conditions—and that some such fission products are involved in the condensation leading to the complex polymeric melanin. Nature fortunately still confronts us with great unsolved problems.

Isotopes are also being pressed into service in our attack on the ills afflicting the animal kingdom. Thus in the fight against a major scourge, carcinogens have been labelled including the nitrogen in 2-acetamidofluorene but so far there are not many definite results to report.

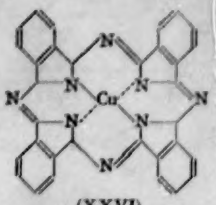
In marked contrast the advances in structural organic chemistry are so numerous and striking that only a few will be mentioned with the object of showing something of the wide range of ring types formed in Nature, before turning to a review of one particular system.



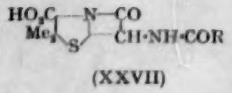
Examples to illustrate the point are many of the B vitamins such as B_1 (XIX), B_2 (XX), the biotins a and b (XXI and XXII), and the linking of the colouring matters of certain butterflies and wasps [leucopterin (XXIII) and xanthopterin (XXIV), respectively] through pteroylglutamic acid (XXV) and B_{12} with the vital subject of nutrition. The fundamental biological importance of *p*-aminobenzoic acid is well illustrated in these compounds.

Porphyrin chemistry is exciting new interest and linked to it are the valuable phthalocyanin

pigments such as **Monastral Blue** (XXVI) whose chemistry was elucidated by Linstead. Recognition of the key function of nucleic acids in cell syntheses adds greatly to the value of the synthetic work being done in this field at Cambridge. The antibiotics such as the penicillins (XXVII) also illustrate the remarkable range of cell syntheses.

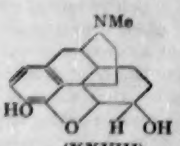


(XXVI)

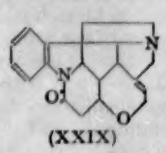


(XXVII)

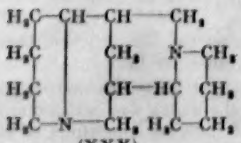
There is intensive activity today in the alkaloid field, both in structural determination and in synthesis: the verification of Robinson's 1926 morphine structure (XXVIII) by Gates and Tschudi (*J. Amer. Chem. Soc.*, 1950, **72**, 228, 4839) and the recent total synthesis of strychnine (XXIX) by Woodward (*J. Amer. Chem. Soc.*, 1954, **76**, 4749, 4751) are remarkable achievements. A glimpse at the structural formulæ of such diverse types as sparteine (XXX), colchicine (XXXI) (whose seven-membered ring structure was largely worked out by J. W. Cook), emetine (XXXII), strychnine, and morphine prompts the remark that all these structures were unravelled by the classical methods without recourse to the newer mechanical aids.



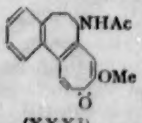
(XXVIII)



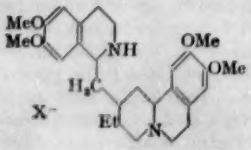
(XXIX)



(XXX)

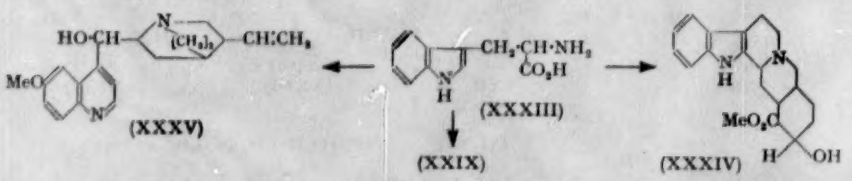


(XXXI)



(XXXII)

The very diverse structural types found in these few alkaloids would appear to render very remote any understanding of their biosynthesis were it not for the fact that Robinson's original essay on this subject (*J.*, 1917, **111**, 876) has now evolved into such a great and powerful unifying conception that, to take one example, such diverse structural types as the yohimbine, *Strychnos*, and *Cinchona* groups of alkaloids can all be based on tryptophan as a common precursor (cf. XXXIII—XXXV).

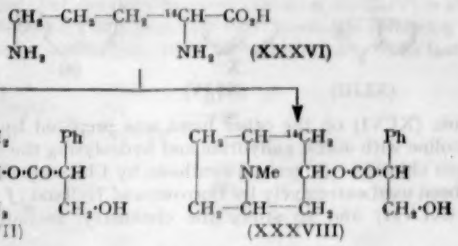


(XXXV) (XXXIII) (XXIX) (XXXIV)

Of much interest is the recent work of Leete, Marion, and Spenser (*Nature*, 1954, **174**, 650) who gave a [^{14}C]ornithine (XXXVI) to *Datura* and obtained non-radioactive hyoscine (XXXVII) and radioactive hyoscyamine (XXXVIII) which on degradation was found to have all the ^{14}C in a bridgehead of the tropine system.

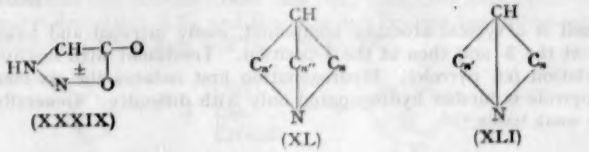
The newer developments in the chemistry of pyrrole, indole, quinoline, and *iso*quinoline are so numerous and have been covered so fully by others that it is not proposed to mention them further here. We may however refer to a number of heterocyclic ring systems, which cannot be

satisfactorily represented by a single formula of the usual valency-bond type, and for which W. Baker and his collaborators (*J.*, 1945, 267; 1949, 307; 1950, 1542; 1951, 289) have proposed the term " mesoionic ". Sydnone (XXXIX) is a typical example.

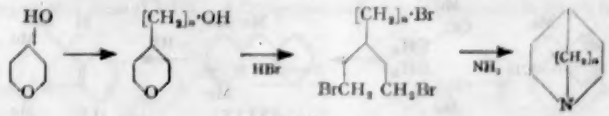


There has been no notable advance in the stereochemistry of organic nitrogen compounds since the classical work of Mills although azo-compounds have been prepared in *cis*- and *trans*-forms. The mechanism of the nitration reaction has been elucidated by Ingold's penetrating work.

We turn now to summarise that less-known chapter in which one or more nitrogen atoms are common to two rings, as in the 1-aza*bicyclo*-[n : n' : n'']- and -[n : n' : 0]-systems (XL) and (XLI). Much of this work is new and a considerable part of it has the merit of being simple and will deserve to be as well-known as is the chemistry of quinoline.

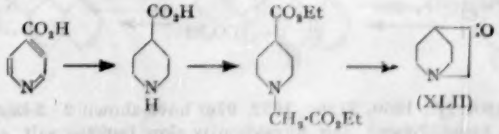


The best known example of the former type is quinuclidine (XL; $n = n' = n'' = 2$) which has only been found in the *Cinchona* alkaloids and a good account of whose chemistry is given by Turner and Woodward in Manske's " Alkaloids," Vol. III; one recalls too the brilliant synthesis of quinine itself by Woodward and Doering (*J. Amer. Chem. Soc.*, 1944, **66**, 879; 1945, **67**, 860), and the curious fact that quinuclidine, although first prepared by Löffler and Stirtzel (*Ber.*, 1909, **42**, 124), was only obtained crystalline in 1920 by Meisenheimer. A more convenient synthesis was effected by Prelog (*Annalen*, 1937, **532**, 69) and this has been adapted as a general method for compounds of this type (see attached scheme).



(n = 1, 2, or 3)

In the same year we prepared 3-oxoquinuclidine (XLII), a compound of evident synthetic possibilities, and converted this into the fully reduced base. The stereochemistry of this system prevents unsaturation at the bridgehead, thus excluding aromatic character, in marked contrast to what is found in the second type (XLI) where fully aromatic compounds are not uncommon. Even here, however, the saturated members of the group are more stable and

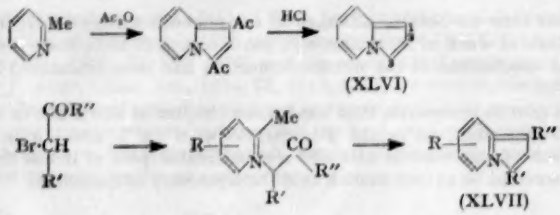


more frequently encountered. Neither pyrrolizine (XLIII) nor its quaternary dehydro-compounds (XLIV) have as yet been prepared; although the keto-derivative (XLV*b*) was easily

obtained as a stable crystalline solid (Clemo and Ramage, *J.*, 1931, 49), all attempts to prepare 1-methylpyrrolizidine [shown by Menschikov to be (±)-heliotridane] by the Grignard reaction and reduction gave only indefinite gums.

(XLIII) (XLIV) (XLV)

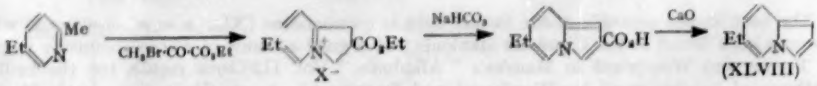
Pyrrocoline (XLVI) on the other hand was prepared by Scholtz (*Ber.*, 1912, **45**, 734) by heating α-picoline with acetic anhydride and hydrolysing the resulting 1 : 3-diacetyl derivative with hydrogen chloride. A general synthesis by Chitschibabin (*Ber.*, 1927, **60**, 1607 and later papers) has been used extensively by Borrows and Holland (*J.*, 1946, 1069; 1947, 670) to obtain derivatives (XLVII) and to study the chemistry, including substitution, of the system.



(XLVI)

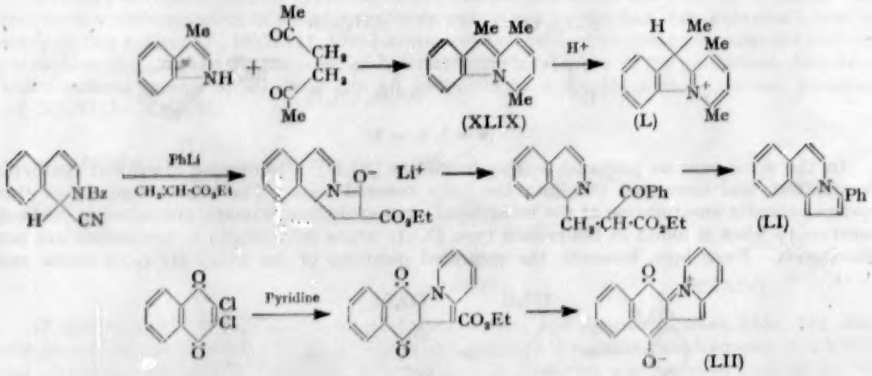
(XLVII)

Pyrrocoline itself is a typical aromatic compound, easily nitrated and halogenated, reaction occurring first at the 3- and then at the 1-position. Treatment with methyl iodide results in nuclear methylation (cf. pyrrole). Hydrogenation first reduces the six-membered ring, and the resulting pyrrole is further hydrogenated only with difficulty. Generally pyrrocolines are yellow and are weak bases.



(XLVIII)

Clemo, Fox, and Raper recently (*J.*, 1953, 4173) prepared 6-ethylpyrrocoline (XLVIII) in the still unsuccessful effort to identify the base $C_{10}H_{11}N$ obtained from strychnine. Various octahydropyrrocolines such as the 2-ethyl and the 1 : 7-dimethyl derivative have been made in the same quest.

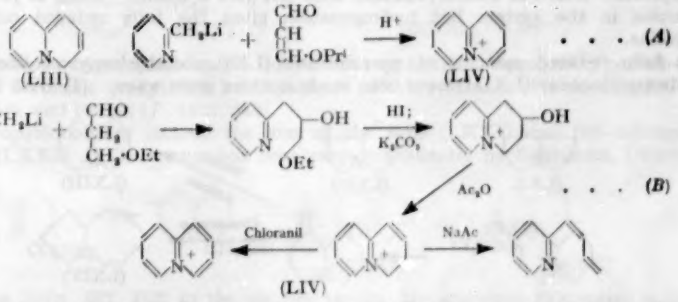


(XLIX) (L) (LI) (LII)

Robinson and Saxton (*J.*, 1950, 3136; 1952, 976) have shown 2 : 3-benzopyrrocolines, *e.g.*, (XLIX), to be weak *pseudo*-bases: salt formation is slow but the salt, *e.g.*, (L) of the much stronger pyridinium base is formed. A recent synthesis of 7 : 8-benzopyrrocolines, *e.g.*, (LI), is that of Boekelheide and Godfrey (*J. Amer. Chem. Soc.*, 1953, **75**, 3679), and an unusual one of

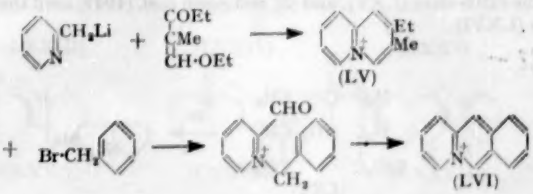
more complex pyrrocolines, *e.g.*, (LII), is described by Pratt, Luckenbaugh, and Erickson (*J. Org. Chem.*, 1954, **19**, 176).

The 6 : 6 ring-system of pyridocoline (LIII) on the other hand cannot be fully aromatic, and all attempts to prepare it have failed, but the dehydropyridocolinium ion (LIV) is aromatic and has been made in two ways—by Woodward and Beaman (1951, quoted in following ref.) (cf. *A*) and by Boekelheide and Gall (*J. Amer. Chem. Soc.*, 1954, **76**, 1832) (cf. *B*). The last stage in (*B*)

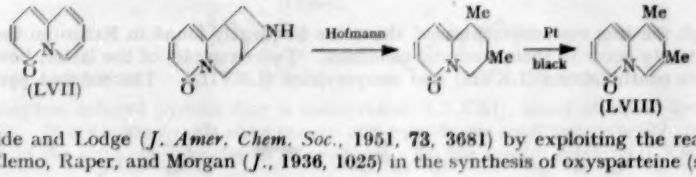


is the nearest approach to a preparation of pyridocoline so far, but this substance seems to be so unstable that it rearranges to 1-2′-pyridylbutadiene.

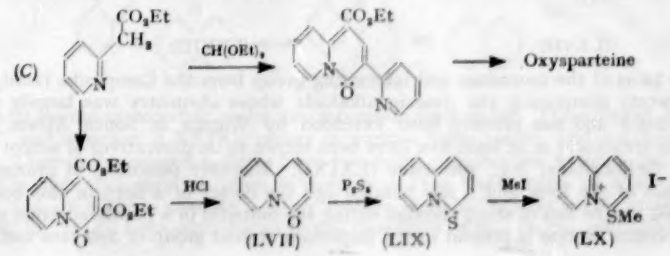
More recently Richards and Stevens (*Chem. and Ind.*, 1954, 905) have extended the reaction to the 2-ethyl-3-methyl derivative (LV), and Bradsher and Beavers have prepared the 1 : 2- and the 2 : 3-benzo-derivative (LVI) (*Chem. and Ind.*, 1954, 1394).



4-Oxopyridocoline (LVII) is also fully aromatic and was obtained in low yield by Späth and Galinowsky (*Ber.*, 1936, **69**, 761) in connection with their work on cytosine in which 1 : 3-dimethyl-5-oxopyridocoline (LVIII) was obtained. A similar dehydrogenation of 4-oxonorlupinane gave the parent base (LVII). 4-Oxopyridocoline was prepared in much better yield by

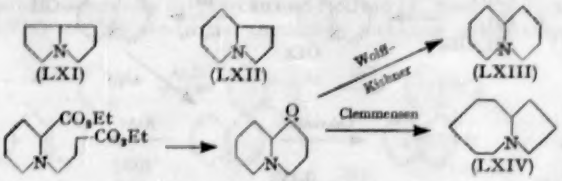


Boekelheide and Lodge (*J. Amer. Chem. Soc.*, 1951, **73**, 3681) by exploiting the reaction first used by Clemo, Raper, and Morgan (*J.*, 1936, 1025) in the synthesis of oxysparteine (scheme *C*).

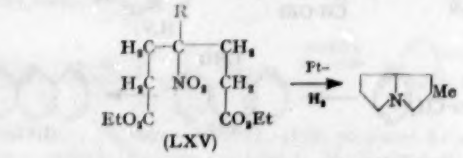


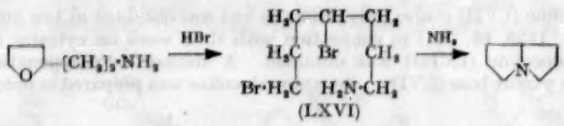
The keto-compound, like its derivatives, forms yellow crystals and shows a marked blue fluorescence in solution. It is extremely soluble in water, and is stable to Grignard-type reagents—an enol-type complex is formed which on acidification liberates the unchanged pyridocoline. With phosphorus pentasulphide the 4-thione (LIX) is formed and this with methyl iodide gives a reactive methylthio-iodide (LX) which readily condenses with malonic ester and with lepidine gives a cyanine dye The presence of substituents greatly changes the reactivity of the system: thus the 6-methyl ketone does not give a thione. Little is yet known about substitution in the system but hydrogenation gives the fully reduced octahydro-4-oxo-pyridocoline.

The fully reduced systems of pyrrolizidine (LXI), octahydropyrrocoline (LXII), and octahydropyridocoline (LXIII) have been made in three main ways. (1) With Dr. Raper and

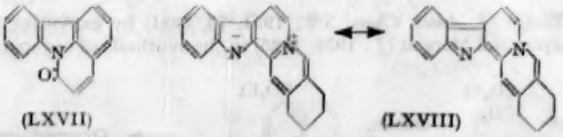


many colleagues we have used the Dieckmann reaction to give a ketone which on reduction by either the Clemmensen or the Wolff–Kishner method usually give the required base. However, we found (*J.*, **1931**, 3190) that whilst reduction of octahydro-1-oxopyridocoline by the latter method gave the desired norlupinane, the former method gave an isomeric base, which Prelog subsequently showed to be the *bicyclo*[**5** : **3** : **0**]-base (LXIV); this is a case of the rare structural change in a Clemmensen reaction. (2) Leonard and his co-workers used reductive cyclisation of the nitro-ester (LXV), and (3) and Šorm *et al.* (1947) used the cyclisation of halogeno-amines such as (LXVI).





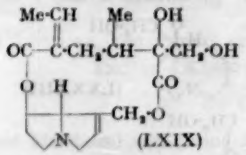
Although the ring systems mentioned above are frequently found in Nature in the reduced form they rarely occur in their aromatic condition. Two examples of the latter, however, are the alkaloids canthin-6-one (LXVII) and sempervirine (LXVIII). The reduced pyrrolizidine

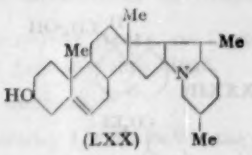


system is the basis of the numerous and interesting group from the Compositæ family (*e.g.*, the common ragwort) comprising the *Senecio* alkaloids whose chemistry was largely developed by Roger Adams and has latterly been extended by Warren in South Africa, with the result that the structures of at least five have been shown to be derivatives of active 1-methyl-pyrrolizidine (heliotridane) [*e.g.*, retrorsine (LXIX)]. Ragwort poisoning of grazing animals causes cirrhosis of the liver and a few months ago the owner of a herd in this country was awarded £4000 for the loss of stock through eating the material in a powdered grass mixture.

The pyrrocoline system is present in the important steroid group of *Solanum* and *Veratrum*

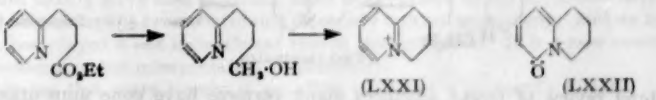
alkaloids whose chemistry has advanced greatly in recent years the potato-shoot alkaloid solanidine (LXX) is a well-known member.


(LXIX)

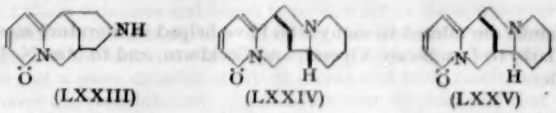

(LXX)

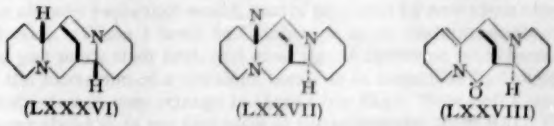
The pyridocoline system occurs as the dehydro-ion or as the corresponding pseudo-base in the well-known berberine group; the best synthesis of this system is still the classical one of Haworth, Koepfli, and Perkin (*J.*, 1927, 548).

The dihydropyridocolines include the ions of the type (LXXI) and the corresponding " pyridones " (LXXII). The former has been prepared recently by Bohlmann, Ottawa, and

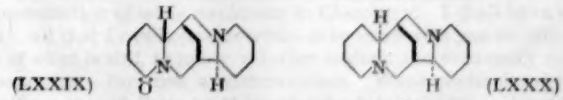

(LXXI) (LXXII)

Keller (*Annalen*, 1954, 587, 162) in the manner shown, but attempts to convert it into the " pyridone " by oxidation under alkaline conditions led to degradation. The pyridone system however is present in the laburnum and gorse alkaloids, cytosine (LXXIII), thermopsine (LXXIV), and anagyrine (LXXV), none of which has yet been synthesised in spite of many

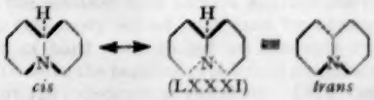

(LXXIII) (LXXIV) (LXXV)


(LXXXVI) (LXXVII) (LXXVIII)

attempts. The hexahydro-derivatives, hexahydrocytosine, α-*iso*sparteine (LXXVI) and sparteine (LXXVII), have however all been synthesised. Aphillidine (LXXVIII) has an oxidation state between anagyrine and sparteine, and reduction gives aphilline isomeric with lupanine (LXXIX).

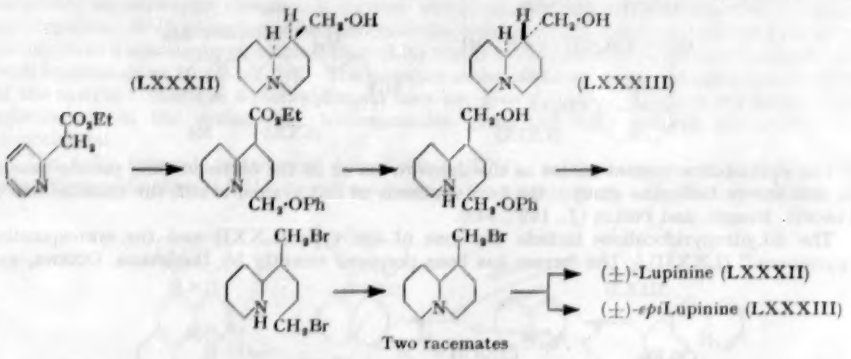

(LXXIX) (LXXX)

The simplest reduced pyridocoline is norlupinane (LXXXI), easily obtained from lupinine (LXXXII). It is not resolvable since the *cis*- and *trans*-forms are interconvertible owing to the oscillation of the nitrogen valencies as in ammonia. In the case of lupinine (LXXXII), how-


cis (LXXXI) *trans*

ever, with its second asymmetric centre two racemates are possible. This alkaloid, with sparteine (LXXVII) and lupanine (LXXIX), occurs in various lupin seeds; and sparteine occurs also in gorse. These fully reduced systems have two fused pyridocoline systems but their stereochemistry is such that only *cis*-fusion is possible so that three forms of sparteine (LXXVI, LXXVII, and LXXX) are possible. Many workers, since Willstätter's early attack on lupinine (*Ber.*, 1902, 35, 1914), have contributed to the chemistry of this group, particularly Karrer on

lupinine, and Ing on cytosine; and with Drs. Raper and Morgan we synthesised lupinine and sparteine (the former is illustrated below), and I had hoped to add lupanine.



In this brief review of recent advances many perforce have gone unmentioned, such as Pauling's great contribution to protein chemistry, the unravelling of the structure of insulin at Cambridge, and so on.

A separate lecture would be necessary to deal with other recent applications of organic nitrogen compounds, of which the use of *iso*nicotinic hydrazide as a tuberculostatic drug is a striking example.

My grateful thanks are offered to many who have helped in literature searches and in other ways, but particularly to Drs. Swan, Vipond, and Cockburn, and to Miss N. Brown, B.Sc., who also made the slides.

The Contributions of Wave Mechanics to Chemistry.

THE TILDEN LECTURE, DELIVERED AT BURLINGTON HOUSE, ON OCTOBER 18TH, 1951, AND IN GLASGOW ON JANUARY 18TH, 1952.

By C. A. COULSON.

WHEN the august Mendeleef was giving his Faraday Lecture before the Chemical Society in 1889, he said :

" While science is pursuing a steady onward movement, it is convenient from time to time to cast a glance back on the route already traversed, and especially to consider new conceptions which aim at discovering the general meaning of the stock of facts accumulated from day to day in our laboratories."

He could hardly have said anything more appropriate to my intention here tonight. We know that Chemistry has been continuing its steady onward movement ; and we know that wave mechanics has played a not insignificant rôle in that progress. It is a new conception and not without meaning in the interpretation of chemistry.

We may see this quite simply if we allow ourselves a moment's history. It was almost exactly a hundred years ago, in the year 1852, that Frankland talked about the " combining power of the attracting element " in chemical combination, and of its " being satisfied by the same number of these atoms," thereby paving the way for the idea of a definite valency for each atom. It was in 1860, only two years after Kekulé and Couper had conceived the idea of some sort of graphical mapping of a molecule, that Odling, and five years later Crum Brown, first drew lines to represent these valencies and began to picture for us the appearance and geometry of an atomic arrangement within a molecule. Halving the time interval we remember that it was only 50 years ago that the electron was discovered at Cambridge, and that this discovery opened up the possibility of a more detailed study of atoms and their resultant molecules. And now we once more halve the time interval. It was just over 25 years ago that wave mechanics was introduced to an already expectant world, partly prepared by new ideas about wave and particle properties in physics. When I went to Cambridge as an undergraduate, a year later, Heitler and London had just made their first, and most signal, incursion into chemistry by showing how we can explain the formation of a covalent bond, as in molecular hydrogen.

Wave mechanics seemed very strange in those early days. How well I recall my own astonishment when I learnt about it, in my first term at the university, from R. H. Fowler, who managed to communicate to me something of his own most evident excitement about it. Yet this strangeness is now passing, and we can look back on these twenty-five years, and can see how wave mechanics has done more than anything else to give us a real understanding of some parts of our subject.

That is what I want to do tonight ; I want to stand back, without fuss or flourish, and try to assess the contribution of wave mechanics to Chemistry. I shall have very little that is brand new to offer : all that I can hope—or wish—is to leave with you an impression, a feeling, of the significance of what is still, to many, a rather esoteric and unsavoury study.

A Misconception.—But first, a misconception. Wave mechanics is not the answer to every chemical problem, though there are those who speak as if it were. When Schrödinger introduced his first paper in the *Annalen der Physik*, he said : " I believe the new method penetrates deeply to the true nature of the quantum rules," and he expressed the hope that it might be fruitfully generalised. So indeed it was. And before long it had become clear that *all* chemical problems could be expressed as the solution to a certain appropriate differential wave equation. But the equation cannot be rigorously solved—not even for atomic helium. And it took Coolidge and James three years of hard work to get an adequate approximate *ab initio* solution for molecular hydrogen. To solve the benzene problem in a similar way we set out with a differential equation involving about 120 independent variables. Dirac could say, in that famous Bakerian lecture of 1929 : " The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known." Yet the true contribution of wave mechanics is not here, as I have to remind myself when I am being urged to start immense schemes for the numerical evaluation of molecular integrals.

But if it is not here, where is it ? The answer is simple. Wave mechanics has shown us what is going on, and at the deepest possible level. We shall find, as we select a few examples, that it has taken the concepts of the experimental chemist—the imaginative perception that came to

those who had lived in their laboratories and allowed their minds to dwell creatively upon the facts that they had found—and it has shown how they all fit together; how, if you wish, they have all one single rationale; and how this hidden relationship to each other can be brought out.

That's a pretty strong claim to make; but I make it. And, if you will let me, I will try to substantiate it. This I will do, by choosing three or four items to illustrate my argument. To some extent they are arbitrary; I apologise for any personal colouring that some of them may have. Let these do duty, then, for all the other examples. I shall not have time to explain them fully, nor to justify what I say; but that will not matter, since it is rather the scope, the insight, the relatedness of wave mechanics to what we may call classical chemistry, which I want to illustrate.

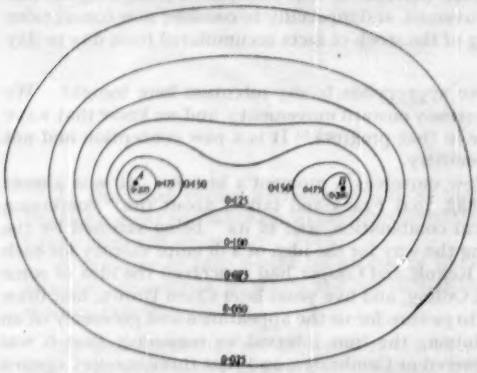


FIG. 1. *Contours of constant charge density for molecular* H_2. *This closely resembles the superposition of separate densities due to isolated* H *atoms except that a certain amount of charge has been attracted from the outer parts of the molecule into the region between the nuclei, where a " plateau " of charge exists at the mid-point.*

The Simple Chemical Bond.—Let me begin, as Frankland, Odling, Couper, and Crum Brown began 100 years ago, with a simple chemical bond. They drew it as a straight line; what do we now believe about it? When Schrödinger introduced his wave mechanics it was recognised that a chemical bond was essentially electronic in origin, and that a normal single bond could be associated with just two electrons. In this we may trace the influence of J. J. Thomson and G. N. Lewis. But how these two electrons moved was a problem quite insoluble within the framework of Bohr's semi-classical quantum theory. It is almost unbelievable to contrast this state of relative ignorance with the detailed picture which is provided by the modern theoretical chemist. In the first place the search for any kind of orbit, in which the path of the electron could be followed from point to point, has been abandoned as conflicting with the Heisenberg uncertainty principle. In its stead we have the picture of a cloud of negative electronic charge; this cloud whose density is simply related to the wave function, spreads out over the bond, embracing both nuclei. We might say that the description of a bond is essentially the description of the pattern of the charge-cloud. There are two electrons, and only two, because the Pauli exclusion principle forbids any two electrons' having the same space-pattern unless they have opposed spins. As there are only two values for the spin variable, this restricts the normal chemical bond to two electrons.

Fig. 1 shows the density pattern for the simplest of all bonds, that of molecular hydrogen. It is astonishing to realise how much information is packed within such a diagram. Thus there is axial symmetry (which is the origin of the almost free rotation around a single bond); there is an approximate size for the molecule, since we can draw a contour, approximately an ellipsoid of revolution, inside which 95% of the total charge cloud will be found; and lastly the charge-cloud itself closely resembles the superposition of appropriate charge-clouds for the individual atoms of the bond except that a quite small, but definite, tendency exists for charge to concentrate in the region between the " nuclei " (*AB* in the Figure) at the expense of charge on the far sides of the nuclei. A simple physical reason exists for this: it is because when an electron is between the nuclei it is being attracted to both, with a gain in potential energy which is sufficient to pull electrons away from the outer regions. It is true, as both theory and accurate *X*-ray analysis have shown, that the additional charge concentrated between the nuclei is usually only in the region of one-tenth to one-quarter of an electron. But this is enough to provide quite a substantial part of the bond energy; and further, because of this tendency for the charge-cloud to be localised between the nuclei, this phenomenon shows us why in a polyatomic molecule, where two electrons in a similar pattern may be used to describe each of the bonds, the bond

properties associated with a bond (*e.g.*, the dipole moment, bond energy, force constant) are largely independent of the molecular environment of the bond in question. We have grown so used to the idea of bond properties, and we find them so useful in identification and classification, that we tend to forget how their existence follows from this account of the shape, size, and localisation of the charge-clouds that I have been describing.

All this insight follows from the wave-mechanical concept of a charge-cloud pattern. As we have seen, these patterns are found from the solutions of the appropriate wave equation. Such solutions are exceedingly difficult to get precisely, and, indeed, in the very last resort, we cannot entirely separate the charge-cloud for one bond from that for another bond. But, subject to certain reasonable limitations, Hund in Germany, Mulliken in America, and Lennard-Jones in Britain have shown that they can be found approximately in terms of suitable patterns (or orbitals, as they are now christened) for the isolated atoms.

FIG. 2. *Charge-clouds of electrons in certain atomic orbitals. The s-type patterns being spherically symmetrical, may be bonded in any direction equally; the p-type, being directed, form strong bonds only along their preferred direction.*

Here we get more light thrown on some famous debates of older days. Between 40 and 50 years ago chemists were much concerned about the problem of whether the affinity of an atom should be thought of as acting centrally in all directions (as would be involved without question in the early ionic notions of Berzelius), or in certain specified directions (as is implied in the models of a tetrahedral carbon atom due to van't Hoff and le Bel). The uncertainty is now very easily removed. Both points of view are right—according to the circumstances—and we can usually tell which description to apply in any given situation. The answer depends on the shape of the atomic orbital out of which the molecular pattern is to be formed. Fig. 2 shows a few of the familiar atomic charge clouds. Some of them are evidently spherically symmetrical, others have a strong directional character. It is not surprising that when an atom, such as H or Li, makes use of one of the *s*-type oribtals to form a bond, the affinity lies equally in all directions; but when, as in O or S, an atom uses two of the *p*-type orbitals, its affinity is located in certain specified directions associated with the axes of the two available *p*-orbitals.

I have purposely used rather old-fashioned language (or perhaps old-fashioned thought-forms) in the above account, because I was anxious to contrast the new account of directional forces in chemical combination with older, pre-wave-mechanical ones. Listen to this, from Werner, about 40 years ago: "The fact that an atom is able to combine with a definite maximum number of atoms is . . . interpreted as meaning that the affinity of an atom only comes into action through a definite number of units of valency, which are considered as independent forces. According to this conception the unit of valency consists of a fraction of the affinity of the atom appearing as an independent force." How much easier, today, to say that these independent forces are the unpaired electrons of the atom, with charge-clouds directed in space with certain mutual relationships (*i.e.*, valency angles) but each permitting the use in conjunction with a suitable charge-cloud from a neighbour atom, in the formation of a molecular pattern of localised electron-pair bonds. But let us continue with Werner: "Some experimenters assume that these independent forces (or units of valency) act only from different positions on the surface of an atom, and that multivalent atoms therefore have their units of valency separated and assigned to definite points on their surfaces . . . the amount of affinity saturated by the linking up of two atoms is distributed on a definite circular segment on the surface of the atom." It was not until the advent of wave-mechanics that we could finally reject this hooks-on-the-surface-of-a-billiard-ball account of chemical bonding.

Another way of relating the directional character of an atomic orbital to its bonding power is to notice that whereas an orbital of *s*-type must overlap any adjacent charge-cloud equally in all directions, an orbital of *p*-type will overlap most efficiently only along its axis of symmetry. What I am describing is the now famous criterion of maximum overlapping, due originally to Pauling and Slater; this is surely one of the most important single principles in the whole of theoretical chemistry, and almost deserves to rank with the Pauli exclusion principle in its profound influence on chemical theory.

Consider, to illustrate the significance of all this, the case of H_2S. Once we recognise that all the electrons in the S atom are fully paired and therefore unavailable for bonding, with the exception of two whose patterns are similar to the p-orbitals of Fig. 2 (strictly 3p atomic orbitals), and that these two orbitals are associated with directions at right angles to each other, as in Fig. 3, then we can see immediately why the HSH angle in H_2S is so close to 90°, with a value of about 92°. It is true that several other refinements would need to be incorporated in this account before it could be said to provide a rigorous demonstration. But what I went to stress is the natural, immediate, almost inevitable character of this and other similar valency angles, once we have grasped quite elementary wave-mechanical ideas.

This leads us to ask about valency angles in carbon. A new feature appears : hybridization. But even this is natural and simple enough if we approach it in the right way, and links on to some of the older view-points. Since the ground state of an isolated carbon atom is described

FIG. 3. *Valence angle in* H_2S. *Each* S–H *bond may be regarded as formed by combination of a hydrogen* 1s *atomic orbital with a sulphur* 3p *orbital. The available* 3p *orbitals are directed at* 90° *as shown on the left. On the right are shown the resulting bond patterns (this is rather schematic, since the detailed shape is not yet known with confidence).*

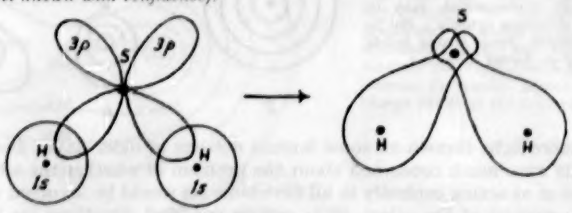
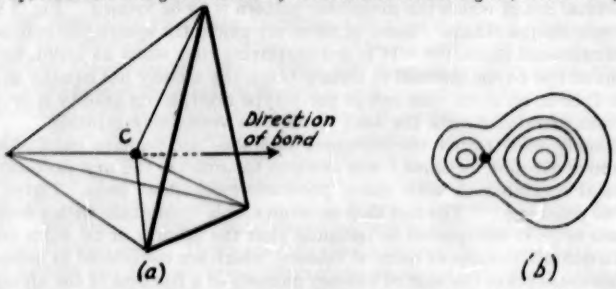


FIG. 4. (a) *Hypothetical division of the charge-cloud of a carbon atom in state* sp^3 *into pyramidal regions (only one of which is shown fully, to avoid confusion), each of which may then be used to form a bond.* (b) *Wave-mechanical version in which the combination of an* s *and a* p *atomic orbital to form a hybrid orbital,* $s + \lambda p$, *leads to a charge-cloud heavily concentrated in one region, similar to* (a).



by the atomic configuration $(2s)^2(2p)^2$, it would be expected to be bivalent. This can be increased to quadrivalency by promoting one of the 2s electrons to a vacant 2p oribtal, to give a configuration $(2s)(2p)^3$. It is interesting to notice that the total charge-cloud associated with these four electrons is spherically symmetrical. The most natural and obvious way of dividing this cloud into parts suitable for building four bonds to adjacent atoms is to divide the spherical charge (Fig. 4a) into regions and to suppose that the charge within one region can be used to form a bond in the direction defined by that region. One symmetrical mode of division provides four regions all equivalent but tetrahedrally oriented with respect to each other. Now what is important for our present purposes is that this procedure is effectively the same as saying that instead of trying to use the original s, p orbitals, we use mixtures, or hybrids, of them. A linear combination of a 2s and a 2p orbital does in fact give a new orbital whose charge-cloud lies almost wholly on one side of the atomic nucleus, and which closely resembles (Fig. 4b) one of the separate regions of charge suggested in Fig. 4a. In such ways as this we begin to see how hybridization appears almost unevitably. Of course there is much more to be said about it than this, but at least the way is clear for us to approach the question of valency angles and bonding in many types of molecular complex. As we all know, a very large degree of order and systematization has resulted from wave-mechanical considerations essentially equivalent to those outlined above. We can see, for example, that if a central atom is to form six bonds to its ligands, these are very

unlikely to be coplanar, but are much more likely to be octahedral; for six coplanar bonds would leave unused a good deal of the charge-cloud (see Fig. 4*a*). We can also see why, if we take different proportions of *s* and *p* in the case of carbon, we shall effectively be dividing up the atomic charge-cloud unequally. So some of our bonds will be stronger than others. In addition the overlapping power of the hybrid will be changed. We should therefore expect a small variation in the covalent radius r_c as the degree of mixing varies. This (Fig. 5) is exactly what is found, the covalent radius changing by several hundredths of an Ångström unit according to the degree of hybridization. This is the origin of many of the small changes in, for example, the length of the C–H bond in aliphatic, olefinic, aromatic, and acetylenic molecules. Carbon is a relatively simple atom to deal with in this way. But Pauling has shown how, in more complex situations such as those that occur in the transition metals and their alloys, the same ideas may be used. Once again I would like to stress the naturalness of this description.

There is another way of looking at this question of stereochemical forces, which is worth mentioning, even though it does not lead to the same quantitative discussion as hybridization. Let us consider carbon again, and suppose that we have an isolated atom with its four valency electrons in the configuration sp^3. These four electrons are described by an atomic wave function ψ which is a function of the four sets of co-ordinates $x_1, y_1, z_1, x_2 \ldots z_4$. We could write it $\psi(x_1 \ldots z_4)$. The probability interpretation of the wave function—which is an alternative to the charge-cloud interpretation, and leads to the same final answers—asserts that the probability of the four electrons' being at the points $x_1 \ldots z_4$ is given by $\psi^2(x_1 \ldots z_4)$. We

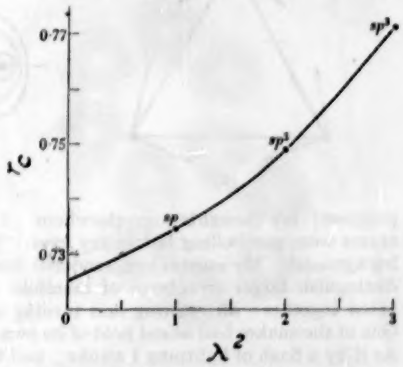


FIG. 5. *Variation of covalent radius* r_c *of carbon with degree of hybridization.* λ *denotes the parameter which governs the relative amounts of* s *and* p *in the hybrid orbital* $s + \lambda p$. *The values* $\lambda^2 = 1, 2,$ *and* 3 *are appropriate for acetylenic, aromatic, and aliphatic carbon.*

may now ask: what are the values of $x_1 \ldots z_4$ which will make this probability greatest? For we could say that these were the most likely relative positions in which to find our four electrons simultaneously. It is not hard to show that the answer is that the most likely simultaneous positions are those of four points tetrahedrally arranged around the nucleus. It is easy to conclude from this that since we are going to use each one of the electrons to form a bond, a tendency will exist for these bonds to be tetrahedral around the central atom. We must not press this type of argument too far, even though, as Linnett, Artman, and Van Artsdalen have shown, it predicts an angle slightly less than tetrahedral in NH_3, where two lone-pair electrons replace one of our previous bonding ones. What this argument does is to give us insight into the way in which the Pauli exclusion principle, by trying to separate electrons with parallel spins, automatically "prepares" the atom for appropriate bond formation. We begin to "feel" why valency angles are what they are.

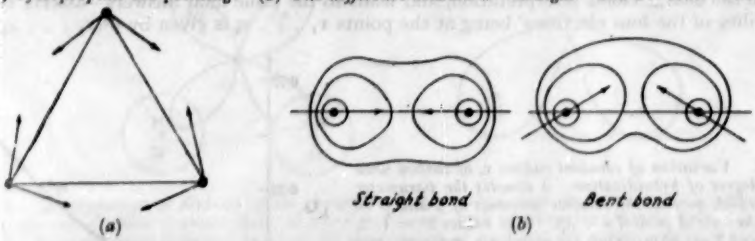
But of course there are occasions in which the geometrical construction of the molecule prevents us from doing what we should like; prevents us, for example, from using hybrids on two atoms A and B which overlap as much as would have been possible without the geometrical constraint provided by the rest of the molecule. A particular case is *cyclo*propane, where the equilateral triangular arrangement of the three carbon atoms compels the valence angles to be 60°. It is easy to show that no satisfactory pair of hybrids can be found in carbon to point at so small an angle. Instead, as Moffitt and the present writer showed several years ago, we have to strike some kind of compromise between the desire to satisfy the criterion of maximum overlapping by using pairs of orbitals directed as nearly towards each other as possible, and to use hybrids with a particularly strong directional character. In the event, it seems that we have to use hybrids which point, as shown in Fig. 6*a*, at an angle of about 22° away from the formal

bond directions. As a result the bond is " bent," and has a charge-cloud somewhat schematically represented by Fig. 6*b*. The significance of this is quite obvious; since the hybrids do not overlap so strongly, the bonds will be weak. An alternative way of speaking is to say that the molecule is strained. But notice how closely Baeyer's early ideas have been translated into wave-mechanical language. We no longer speak of elastic threads being bent: but we speak of a charge-cloud lacking axial symmetry, and of wasted overlapping power. And what is more, we can calculate the strain.

One further point emerges very naturally from this discussion. Since the electrons on atoms A and B are such that their charge-clouds do not overlap to the maximum degree possible, it follows that they are more loosely coupled in establishing one of the carbon–carbon bonds. This, for reasons that will appear later, is an explanation of the familiar conjugating power of the *cyclo*propyl group, when placed next to a double bond, as in *cyclo*propylethylene.

π-Electron Chemistry.—The time has come to turn to a rather different application of wave mechanics—what we loosely call resonance in organic unsaturated and aromatic molecules. Listen first to these familiar words of Kekulé. They were written in 1865, during his tenure of the chair of Chemistry at Ghent: " I was sitting writing at my text-book, but the work did not

FIG. 6. (a) *Arrows denote the directions in which the hybrids which are to be used in forming the* C–C *bonds of* cyclo*propane are pointing.* (b) *The difference between a " straight " and a " bent " bond.*



progress; my thoughts were elsewhere. I turned my chair to the fire, and dozed. Again the atoms were gambolling before my eyes. This time the smaller groups kept modestly in the background. My mental eye, rendered more acute by repeated visions of this kind, could now distinguish larger structures of manifold conformation; long rows, sometimes more closely fitted together; all twisting and turning in snake-like motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightning I awoke; and this time also I spent the rest of the night in working out the consequences of the hypothesis." Now it is quite true that the vision of a snake seizing hold of its own tail was not new. As Professor Read has pointed out, it is " a symbol in ancient Egypt of eternity, a symbol in ancient Greece of the Platonic idea of the unity of matter, and a symbol among the alchemists of rejuvenation." It was also a symbol for the early Celtic Christian Church. What Kekulé had seen in this evening vision was, of course, the closed-ring structure of benzene. But what he saw, as it were " in a glass darkly," has been taken up by more modern wave mechanics. For that closed ring of carbon atoms implied the possibility that tiny electrical currents might flow around the ring: and those snakes of his that bit their tails were the prototype of what we now call delocalized molecular orbitals, charge-cloud patterns such as that in Fig. 7 which extend all round the ring, and suggest that an electron in such an orbital may be found at any one of the atoms of the ring. Here, in fact, is the beginning of an explanation of the remarkable power which planar aromatic molecules possess, of transmitting electrical influences from one region of the molecule to another. It is true that only some of the valency electrons—the so-called π-electrons—are to be treated like this. But it is easy to see which they are, and to calculate approximate energies and charge distributions for them. And with this concept there comes automatically the proper description of the molecular shape, and the abandonment of the Ladenburg prism formula, and the other models of Claus and Armstrong and others.

Several other things follow from all this very simply. For example there is the regular-hexagonal nature of the benzene ring, with all its sides equal. We all know what a puzzle this was to the older chemists, and how attempts were made to satisfy the chemists' feeling that all the C–C bonds must be equivalent, by supposing some sort of dynamic oscillation between what are now called Kekulé forms. All this has gone: and in its place we show from the nature of

the molecular orbitals for the π-electrons that all the bonds should be equal in the ground state, though in some of the possible excited states this may no longer be true.

I cannot forbear, however, from recalling how, in one sense, Kekulé presaged a way of looking at these conjugated and aromatic molecules which was to be taken up and developed properly only when wave mechanics was available. I am thinking of the notion of resonance, developed in this connection particularly by Pauling. It is still possible to think in terms of Kekulé structures (and Dewar structures of course also): but these structures do not have the independent objective existence which Kekulé supposed. Instead, we think of them as possible ways in which we could start with the π-electrons on their separate atoms and then pair them together to form bonds. There are many ways of doing this: each of them corresponds to a Kekulé or other structure: and all must be regarded as existing at the same time, losing their individuality in the resonance that I have been describing. In some respects it is not unlike the way in which yellow and red make brown, a new colour which is not like either of its parents, though it may be regarded as derived from both. At this distance of time it is nothing less than amazing that Kekulé could have argued as he did.

FIG. 7. *A somewhat schematic representation of a π molecular orbital in benzene. The charge-cloud consists of two regions, of streamer-like character, above and below the molecular plane, and extending over all six carbon atoms.*

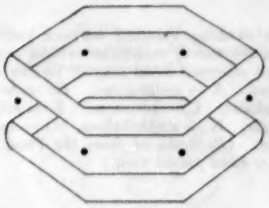
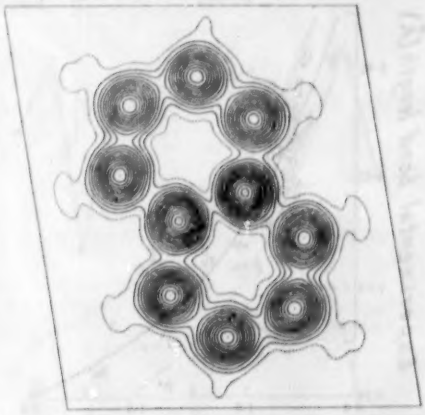
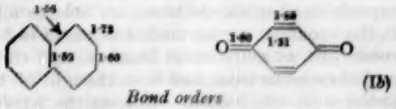


FIG. 8. *Charge-density contours for naphthalene. (Prof. J. M. Robertson; reproduced by kind permission from* Acta Cryst.)



But there is more to say about all this. In benzene all the C–C bonds are similar; but in naphthalene they are not. Their actual values may be found experimentally from the accurate *X*-ray diagrams of charge density such as Fig. 8, obtained by Professor J. M. Robertson. What can we say theoretically about patterns of this kind? In the first place, as Dr. N. H. March has shown, it is possible to calculate, in advance, diagrams of the total charge distribution which very closely resemble that of the Figure. In particular, it is possible to assign to each of the C–C bonds a numerical magnitude—what Lennard-Jones called its bond order. This is 1, 2, and 3 for single, double, and triple bonds, with intermediate fractional values for other types of bond. If the bond order p is large, the bond can be said to possess more double-bond character than if it is small. In this way we see new light on another very old question, bond fixation. Despite great attempts to do so, the older classical chemists were unable to show unequivocally that in a molecule such as naphthalene, the 1–2 bond was really either double, or single. It appeared to be more double than single; and so the attempt was made to speak of bond fixation



Bond orders

Now however we see that bond fixation is never absolute. All that we can say is that there is a relative degree of double-bond fixation: and we can give figures to show how large this is. Thus in naphthalene (I*a*) there is much less bond fixation than in benzoquinone (I*b*), though even in the latter molecule it is not absolute.

Now if two bonds differ in bond order, we should expect them to differ in bond length. The lengths of the C–C, C=C and C≡C bonds are **1·54**, **1·34**, and **1·20** Å respectively. It should therefore be possible, as Pauling first showed, to draw a curve relating order and length, and use this curve to predict unknown bond lengths once the corresponding bond orders have been calculated. It is significant that when a smooth curve is drawn through the points corresponding to single, double, and triple bonds, benzene (order **1·67**, length **1·39** Å) and graphite (order **1·52**, length **1·42** Å) fit excellently on to it. Fig. **9** is a composite diagram showing all the calculated orders and observed lengths for the molecules listed underneath it. There can be no doubt but that this graph justifies the concept of fractional bond order, and shows how we may use the theory to predict bond lengths. The two broken lines of the diagram are drawn parallel to the central one, at a distance **0·02** Å from it. When it is realised that almost all the observed point lie within the band thus formed, and that the experimental accuracy of most of these points is only ±**0·02** Å, we can see how satisfactory the wave-mechanical argument really is. In larger molecules the agreement seems to be even better than in small, as the situation shown in Figs. **10** and **11** for ovalene illustrates very nicely. This is an agreeable situation, but one that is unfortunately not very common in Science.

The concept of fractional bond order is one of the most fruitful of the concepts which wave mechanics has introduced and developed. As we shall see later, it may be used very profitably

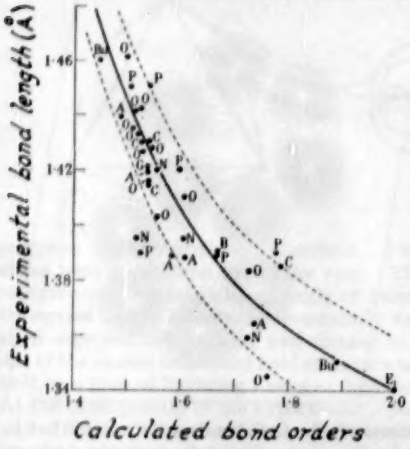


FIG. 9. *Curve showing relation between calculated bond orders (by use of molecular-orbital approximation) and observed bond lengths in conjugated hydrocarbons.* A = *anthracene*, Be = *benzene*, Bu = *butadiene*, C = *coronene*, E = *ethylene*, G = *graphite*, N = *naphthalene*, O = *ovalene*, P = *pyrene*. (*Reproduced from the* Proc. Roy. Soc., *A., by kind permission.*)

in the study of certain types of chemical reactivity, as well as in discussions of structure such as that I have just given. But of course it was not original to wave mechanics. Had not Ingold described a mesomeric effect and had not Robinson and Lapworth attempted graphically, by the now familiar curved arrows, to represent some flow of bonding power from one region to another in a molecule ? Yet I believe it is perfectly true to say that without this contribution from the theoretician, it would have been very difficult to see really what was involved in the curved arrows and the mesomerism.

There is one other famous discussion of older days to which I want to refer before we leave the discussion of π-electron chemistry. This is the famous " aromatic sextet " rule. Within two or three years of G. N. Lewis' papers on the electron-pair bond it came to be realised that in stable benzenoid systems there appeared to be a total of six electrons forming some sort of stable grouping. In 1918 Sir Rob ert Robinson stated that " the characteristics of all benzenoid systems is to be sought in the hypothesis that six electrons are able to form a group which resists disruption." This group is the aromatic sextet, and it is found in heterocyclic molecules such as pyridine, furan, and pyrrole just as much as in benzene, and the *cyclo*pentadienyl anion. At this distance of time, long before π-electrons had been thought of, the hypothesis of an aromatic sextet can only be regarded with admiration. But, at the hands of people like Hückel, this hypothesis has received an exceedingly simple explanation in terms of the molecular orbitals of the ring. Fig. **12** shows the energy levels for the π-electrons in a ring containing **5**, **6**, or **7** identical atoms. (If one or more of the atoms differs from the others, the details of **Fig. 12** are changed, but not the main argument which follows.) All levels below the central broken line may be regarded as bonding, and there will be a tendency to fill them with as many electrons as

they can contain. All levels above that line are anti-bonding, and a molecule will try to shed any electrons which may happen to have been forced into these levels because there were no other lower levels available. It is clear from the Figure that all three systems can accommodate six electrons in bonding orbitals. Hence the explanation of $C_5H_5^-$, C_6H_6, and $C_7H_7^+$. The whole discussion is so simple as to be almost obvious. But that, surely, is one of the characteristics of a good explanation.

There are very many examples to illustrate the general rule, that a six-ring of carbon atoms will not readily give or receive additional electrons, and that a five-ring will accept and a seven-ring will donate an electron. For example it is now known that in fulvene (II) there is a dipole moment of about 1 D due to migration of electrons from the ethylenic double bond into the five-membered ring. In azulene (III) the dipole moment is probably larger, owing to donation from the seven-membered and simultaneous acceptance by the five-membered ring. The non-existence of the hypothetical molecule pentalene (IV) is probably due just as much to the fact

FIG. 10. *Ovalene* $C_{32}H_{14}$, *showing the naming of the* 12 *essentially different C–C bonds.*

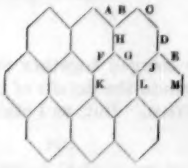
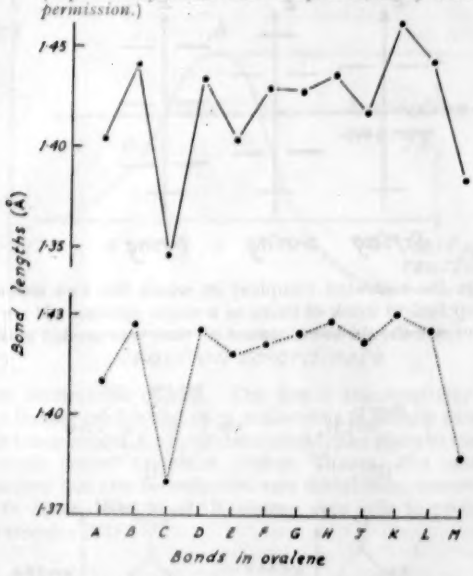


FIG. 11. *Comparison between computed and observed bond lengths in ovalene.* —— *X-Ray measurements of Prof. J. M. Robertson;* – – – – *Molecular-orbital calculations of Miss Buzeman (Mrs. Taylor).* (*Reproduced from the* Proc. Roy. Soc., *A, by kind permission.*)



that both five-membered rings are seeking for electrons, and that there is no source of supply, as to the more sophisticated explanations that can, and have, been given. This suggests that a possible stable molecule of this type would be a polymethylpentalene, where the electron demands of the central rings were met by the donor methyl groups round the perimeter. In the same way the ferrocene system—or molecular sandwich, if we adopt the term introduced by Orgel and Dunitz—in which an iron atom lies midway between two parallel C_5H_5 groups, is readily understood if it is written as $C_5H_5^-{\cdot}Fe^{++}{\cdot}C_5H_5^-$ (the detailed relations of the ions here cannot, however, be explained without more intimate study, of the kind recently described by W. E. Moffitt). But the system itself is of very general character, as is shown by the existence of similar sandwiches in which Fe is replaced by Ti, Zr, V, Nb, and Ta.

One final example of the aromatic sextet will show how widespread is its use. The hydroxy-*cyclo*heptatrienyl bromide molecule is found in solution in the form (V) where the positive charge seems to lie in the seven-membered ring and not particularly on the hydroxy-hydrogen atom. Similarly the dipole moment of tropone (VI) is much larger than that of a normal carbonyl group, as, *e.g.*, in benzoic acid (VII), indicating the relatively greater importance of ionic structures such as (VIII) for tropone than for benzoic acid.

It may be interesting to point out that there is an aromatic duplet, as well as an aromatic

sextet, though this is less often noticed. Some recent calculations of charge in the methylene-*cyclo*propene molecule (IX) show that charge has left the three-membered ring and migrated to the exocyclic carbon atom, in distinction to the situation in fulvene (II) where it leaves the exocyclic carbon atom and migrates into the ring.

Chemical Reactivity.—And now we must leave questions of chemical structure in order to deal with the last of my three main applications of wave mechanics : chemical reactivity. This is a wide field and some choice of material is inevitable. I propose therefore to leave out of my account any mention of the interesting and valuable work of Eyring, Polanyi, and M. G. Evans on the reactions of saturated systems : and shall instead deal only with the reactions of π-electron molecules where, on account of the common fundamental possession of these π-electrons, a greater degree of systematization is possible In this field, as in our earlier fields, we shall see how naturally modern wave mechanics has gathered up the older ideas and fitted them into a most promising general scheme.

We must begin, as all discussions of reactivity must, by a reference to the reaction-path diagram (Fig. 13) of Eyring and Polanyi. Here, between the initial and the final stage we may distinguish (*a*) the perturbed (or polarised) stage in which the reacting systems, while still separate and distinct from each other, have nevertheless begun to polarise each other, and (*b*) the transition

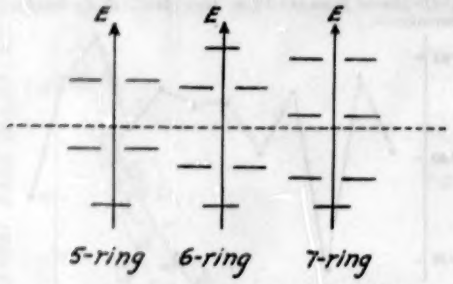
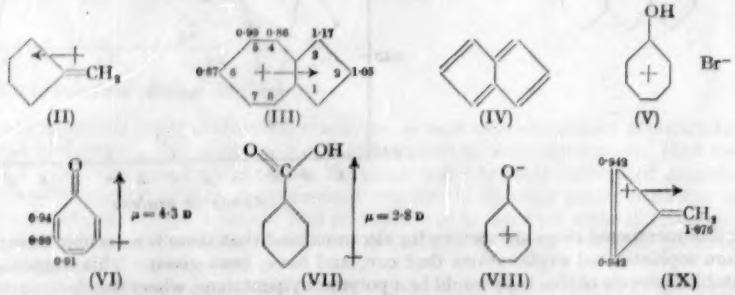


FIG. 12. *Calculated energy levels for the π-electrons in 5-, 6-, and 7-membered rings. All levels below the broken line are bonding, those above it are anti-bonding. The tendency to acquire the aromatic sextet of electrons in all three cases follows from the fact that there are just three bonding levels, which can hold six electrons. (Many of the levels, as shown in the diagram, are doubly degenerate. Each such level will hold 4 electrons in all.)*

stage (or activated complex) in which the two molecules have merged together and we are compelled to think of them as a single system. If we could calculate the details of this energy curve, we should know almost all that was needed about the reaction. But, as I stated earlier,



(In these formulæ arrows denote the direction of migration of the π-electrons, and the numerical values at each atom give the total number of π-electrons associated with that atom. Values not shown follow from symmetry.)

such a hope is doomed to disappointment. Instead, we shall ask, in more modest mood, what influences are responsible for the changes in energy associated with (*a*) the perturbed and (*b*) the transition state. If we can get an answer to these questions—as indeed we shall see that we can—then we can make good our claim that wave mechanics has helped us to see and to feel what is going on in a reaction of this kind.

It is clear that any discussion of this sort must start by distinguishing the heterolytic and the homolytic type of reaction. In the first, at least one of the reagents is essentially ionic, and in the second both are normally uncharged free radicals, though of course there may be some polarity in them associated with the presence of polar groupings. The distinction between these two types of reaction is, of course, equally preserved in the wave-mechanical analysis. We shall find it convenient to deal with the heterolytic type first.

A large number of heterolytic reactions are covered by two rules : (i) a positive (*i.e.*, electrophilic) reagent will attack that part of the molecule where the negative charge is greatest, and (ii) a substituent in any conjugated system such as benzene induces alternately greater and less reactivity at the successive atoms on either side. The first of these rules is the original rule of Robinson and Lapworth, the second is one form of the law of alternating polarity, or alternating affinity, associated first with the name of Flürscheim. Both of these rules may now be put in wave-mechanical language. Thus Professor Longuet-Higgins and the present writer have shown that when a positive charge approaches one position (C_r say) in a conjugated molecule, its electric field may be supposed to pull any electrons that are free to move, towards C_r. These are the π-electrons, and the pull towards C_r may be translated into the statement that this particular atom has an enhanced electronegativity. It is not difficult to calculate the energy change associated with this change of electronegativity, and so we can estimate the change in π-electron energy when the original cation approaches C_r. It turns out that the term which dominates this change of energy is none other than the total π-electron charge on C_r before the reaction started. This means that the early stages of the reaction are governed by the charge distribution. But this is precisely our rule (i). For nucleophilic reagents the attack comes most easily at that carbon atom where the number of π-electrons is least.

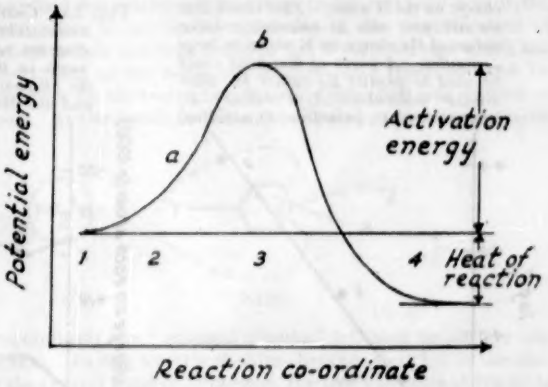
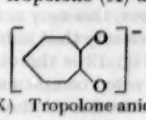
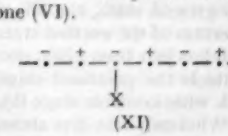


FIG. 13. *A potential-energy curve for a chemical reaction, showing the four stages* (1) *initial reactants,* (2) *perturbed (polarised) or* (*a*) *stage,* (3) *transition (activated) or* (*b*) *stage, and* (4) *final products.*

Before going further we may give two illustrations of this. The first is the reactivity of azulene. According to structure (III) the largest concentration of π-electrons is around atoms $C_{(3)}$ and its equivalent $C_{(1)}$. We should therefore expect that nitration would take place at these positions. In fact this prediction was made before Anderson, Nelson, Tazura, and others showed experimentally that not only nitration, but also bromination and acetylation, occurred at the 1-position. In the same way R. D. Brown and M. J. S. Dewar were able to predict nucleophilic activity in tropolone (X) and tropone (VI).



(X) Tropolone anion



(XI)

The second example that I have chosen is one where accurate numerical comparisons are possible. It is well known that the silver cation very readily forms complexes with nitrogen compounds. Fyfe has measured the equilibrium constant K_f for a series of amines, where the reaction is

$$Ag^+ + 2Amine \rightleftharpoons (Ag\ Amine_2)^+$$

and

$$K_f = (Ag\ Amine_2)^+/(Ag^+)(Amine)^2.$$

We may expect that, other things being equal, equilibrium will lie more to the right if the N atom, which is to form an ionic bond to the metal atom, carries as large a number of electrons as possible. The charge on the N atom in such molecules as pyridine, quinoline, and acridine can easily be calculated, and even if the values shown in Fig. 14 are not absolutely correct, they are almost certain to be relatively so. It will be seen that when the experimental values of log K_f are plotted against the theoretical charge, a good straight line results. This is just what

would have been expected, and shows us that we may use complex-forming ability as a kind of "charge probe." And surely the conclusion of all this is that we are beginning to understand the distribution of electrons in these heteronuclear molecules in a deeper sense now than would ever have been possible before.

The second fundamental rule—rule (ii) above—was expressed in the law of alternating polarity. Here it has proved possible to give a very general theoretical discussion. It has been shown, for example, that if we take a long conjugated polyene chain such as (XI) and then replace one of the H atoms by a substituent X, there will be migrations of charge which lead to a final situation in which the atoms are alternately positively and negatively charged as we move away from X in either direction: and in which the net charges on the atoms diminish with distance from X. For example, if X attracts charge from its adjacent carbon atom, the resulting migrations of π-electron charge in the conjugated chain will follow the distribution of signs shown. Now this is precisely the law of alternating polarity for a straight chain. For benzenoid systems it still holds, though since we can get to the *para*-position in benzene by two routes, the dying-away effect is less pronounced. Fig. 15 shows the π-electron charges induced in stilbene

FIG. 14. *The variation of diamine formation constant K_f with theoretical charge on the N atom. This shows that we are now able to calculate relative values of the charge on N atoms in large molecules. A curve of this kind could be used to predict K_f values for other similar molecules. A, Pyridine; B, isoquinoline; C, quinoline; D, acridine.*

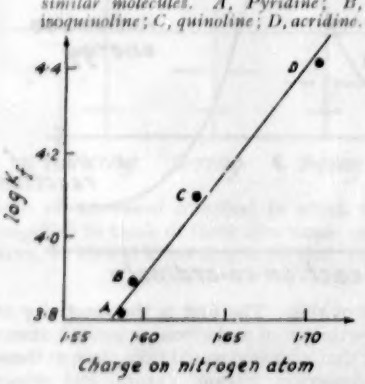
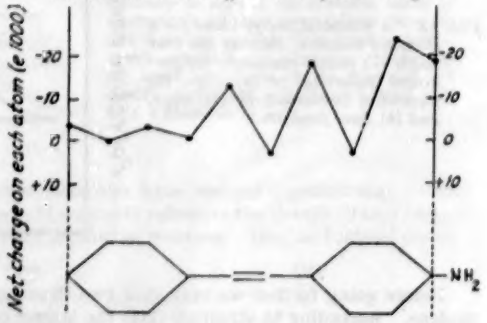


FIG. 15. *Charge distribution for the π-electrons in 4-aminostilbene. The charges shown in the top diagram relate to the carbon atoms directly underneath in the lower diagram. This diagram shows the alternating character of the charge distribution, and also the minute effect in the farther ring.*



(where originally they are all closely equal to 0) by an amino-substitution in the 4-position of one ring. It is surely most interesting that we can not only trace the alternating charge effect, but also see that in the ground state, the effect of the substituent is hardly appreciable in the far benzene ring. In certain of the excited states, however, this may not be the case.

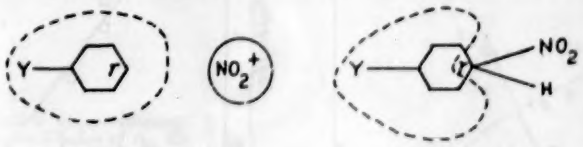
The discussion which has just been given shows very clearly that in heterolytic reactions, the factor which really controls the polarised stage (*a*) of Fig. 13 is the charge distribution. We may reasonably now ask what controls stage (*b*), the activated complex stage. Here the answer has been provided by Wheland, who has shown that estimates of the difference in activation energy as between one position of attack in a molecule and some other position in the same molecule or in some other molecule, may be found by the following localisation process.

Let us consider the approach of an NO_2^+ group towards atom C_r of an aromatic system (XII*a*). As Ingold has shown, this is the first step in an aromatic nitration. In the transition state we may imagine a bond formed from C_r to the NO_2^+, as in (XII*b*). This bond requires that C_r becomes a tetrahedral atom, so that the resonating region of the molecule is effectively restricted to that part within the broken line. Further, since the new bond uses two electrons, the total number within the resonating region is now two less than it was before. Consequently the π-electron energy is altered, and the extent of this alteration provides a good measure of the activation energy, since the other energy effects which most certainly exist—change of σ-bond energy, change of hybridization at C_r, formation of C_r–NO_2 bond—may be presumed to be constant both for different atoms r and even for different molecules. If we may describe the difference in π-electron energy between (XII*a* and *b*) as the localisation energy, then differences in localisation energy should be closely similar to differences in activation energy.

A single example, taken from Wheland's work, will suffice. If Y in (XII*a*) is itself a nitro-group, we are concerned with the nitration of nitrobenzene. We could imagine that the second nitro-group approached to the *ortho-*, *meta-*, or *para*-position in (XII*a*). Wheland shows that the localisation energies necessary to produce the transition states (XII*b*) are **1·886**, **1·852**, and **1·861** respectively, measured in terms of a certain fundamental resonance integral β. The lowest of these is the middle one, showing that *m*-dinitrobenzene is formed more easily than the *o*- or *p*-isomer; and, by comparison with the figure for benzene itself (**1·814** β) we can see that the first nitration of benzene requires less activation energy than the second.

All this fits together very nicely; and considerable extensions, to deal with attack at a bond rather than an atom, and also with the Diels–Alder diene addition, have been made by R. D. Brown and others. We are justified in claiming that in heterolytic reactions the dominant factor in stage (*b*) of Fig. 13 is the localisation energy. By good fortune it turns out that predictions made on the basis of polarisation calculations, as in stage (*a*), almost always agree with predictions on the basis of localisation calculations, as in stage (*b*). This agreement justifies us in our belief that the model with which we try to understand this type of reactivity, is adequate and basically correct.

Our discussion of the second type of reactivity can now be quite short; for many of the same basic ideas which have just been described for heterolytic reactions carry over into homolytic, *i.e.*, free-radical, reactions. However, there is one major difference in our consideration of stage (*a*). It is not really a new concept which has been devised, but a very old one which has been brought up to date. At the beginning of the twentieth century, as a result of work by Flürscheim, Thiele, and Werner, there grew up the conviction that any one atom was capable of exerting only a certain definite affinity. If the bonds to this atom were already using up most



(XII*a*) (XII*b*)

of this affinity, there would be correspondingly less "residual affinity" left over to initiate any possible substitution or addition reaction. In this way these older chemists were led to the idea of a free valency. Sometimes, as in the central bond of butadiene, the free valencies at the ends of a bond managed to satisfy each other; but at other times, as with the terminal carbons in butadiene, this was not possible, and the molecule would be reactive at these positions. What does wave mechanics have to say about this model? The interesting point is that it has justified nearly every one of those earlier claims—in the appropriate circumstances. For example, it has shown that there really is a total affinity for an atom: in modern terms there is a maximum possible value for the sum of all the bond orders of the bonds which terminate on that atom. In the case of carbon this maximum value is $3 + \sqrt{3} = 4{\cdot}732$. If we add together the fractional orders of all the bonds in a given molecule, we can soon see by how much the total bond number for any atom is less than the maximum possible. This is the free valence, or residual affinity. It is a reasonable hope that this affinity would be available for the initiation of any additional bonds that might be necessary in the course of a chemical reaction. But it is equally probable that the reactions to which it would be expected to apply best would be free-radical ones, where a radical with an unpaired electron can come quite close to the original molecule, and begin the formation of an incipient bond, without the intervention of large localised charges and their associated Coulomb forces. It is true, of course, that in nearly all cases there will be a small amount of unbalanced positive and negative charge, whose effect would be to modify our simple picture by superposing on it a small heterolytic character. But in cases where, for example, a Ph or CH_3 radical approaches a pyridine molecule, we should expect that the dominating influence would be the free valence. A great merit of this new development is that, since we can now calculate actual bond orders numerically, we can give a numerical value for the residual affinity. In this respect, not only has wave mechanics vindicated the older views: it has extended them by allowing comparisons between different molecules, and different positions in the same molecule.

Two short examples will make this clear. In naphthalene (I*a*) the total bond number for $C_{(1)}$ is **1·56** + **1·73** + **1·00** (C–H bond) = **4·29**. Thus the free valence is **4·732** − **4·29** = **0·44**. But for $C_{(2)}$ the total bond number is **1·73** + **1·60** + **1·00** = **4·33**, leading to a free valence **0·40**. We

may therefore expect that the 1-position would be just a little more reactive towards free radicals than the 2-position. But the difference would not be very large. This is a general conclusion. For example it may be shown that in a monosubstituted benzene the free valences at the *o*-, *m*-, and *p*-position will always be such that $o, p > m$, though once again the differences will not be expected to be large. We should not be surprised therefore that all three positions are usually substituted, and, as Hey and Waters and Weiss have shown, *ortho*- and *para*-compounds are formed rather more easily than the *meta*-compound.

My second example shows the power of this type of calculation to give an accurate numerical account of the relative ease of free-radical attack on a series of molecules. Kooyman and Fahrenhorst at Amsterdam have made experiments in which a CCl_3 radical is used competitively, either to attack keten and continue a chain reaction, or to attack an aromatic hydrocarbon such

FIG. 16.

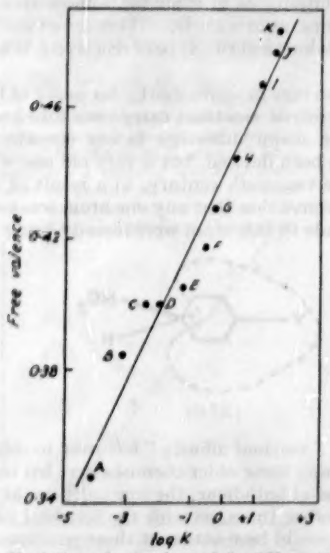


FIG. 17.

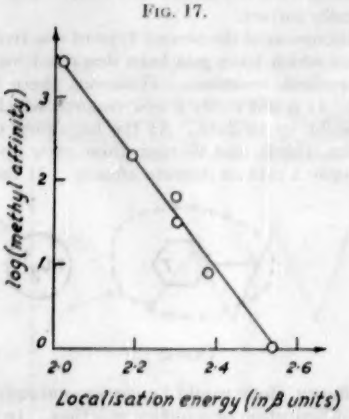


FIG. 16. *Variation of rate of attack by CCl_3 radical on various hydrocarbons plotted against calculated free valence. Experimental points were obtained by Kooyman and Fahrenhorst. This curve illustrates the way in which the free valence, i.e., residual affinity, governs free-radical reactions. A, Benzene; B, diphenyl; C, phenanthrene; D, naphthalene; E, chrysene; F, pyrene; G, stilbene; H, dibenzanthracene; I, anthracene; J, naphthacene; K, benzanthracene.*

FIG. 17. *Curve showing the linear relation between log (methyl affinity) of a series of aromatic hydrocarbons and the calculated localisation energy. The reaction is* $Me + A \longrightarrow MeA$. *The observed fit of the experimental points on a straight line shows that the transition state is adequately described. It also enables us to decide at what part of the molecule the methyl group becomes attached.*

as anthracene or chrysene. Since the reaction is competitive, by suitable choice of conditions and measurement of the degree of polymerisation, we can compare rates of this reaction with different hydrocarbons. Fig. 16 shows what an excellent straight line links the logarithm of the observed rate with the calculated free valence. It is indeed most gratifying that this relation holds for molecules as diverse as benzene with one ring and dibenzanthracene with five. It seems clear that we begin to understand the really essential factors in stage (*a*) of a homolytic reaction.

So far as stage (*b*) is concerned, the analysis is similar to that already described for heterolytic reactions. Let us suppose, for example, that in (XII*a*) we were bringing up a neutral free radical such as methyl to carbon C_r, instead of the positively charged NO_2^+ ion shown in the diagram. Structure (XII*b*) would be essentially the same, except that there would be one additional electron within the resonating part of the molecule. We should, in general, require a different localisation energy from the previous one, though we might expect to find a variation of the logarithm of the rate with the new localisation energy similar to that illustrated earlier for heterolytic reactions in Fig. 14. Fig. 17 shows some very recent results due to Levy and Szwarc. These authors considered the attack of methyl radicals on a variety of hydrocarbons,

and were able to infer the existence of a relative methyl affinity for the reaction : A + Me ⟶ MeA, where A is an aromatic hydrocarbon. The plot in Fig. 17 shows conclusively that there is an almost strictly linear relation between the logarithm of the methyl affinity and the localisation energy. A curve of this kind could evidently be used to predict methyl affinities for molecules as yet not studied experimentally. And so once more wave mechanics has helped us to understand things which otherwise we could scarcely have hoped to regularize in so effective a manner.

There is still much for us to learn about chemical reactivity, and probably there will be new models to improve on the ones which I have just been describing. But whatever they may be in detail it seems almost inevitable that they should be essentially wave-mechanical in their general approach. Indeed no one can reflect on the progress that I have been describing in these last few pages without recognising that, at last, we are on the way to systematizing chemical reactivity just as earlier we were able to systematize valency and stereochemistry.

FIG. 18. *Molecules showing the* K*-region. Anthracene has no* K*-region but phenanthrene and benzacridine have. Carcinogenic activity seems to depend on the electronic distribution in and near this* K*-region*

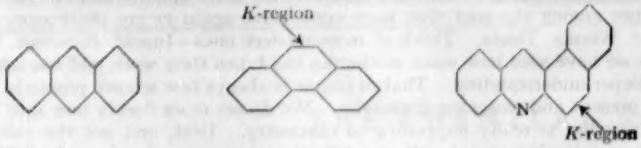
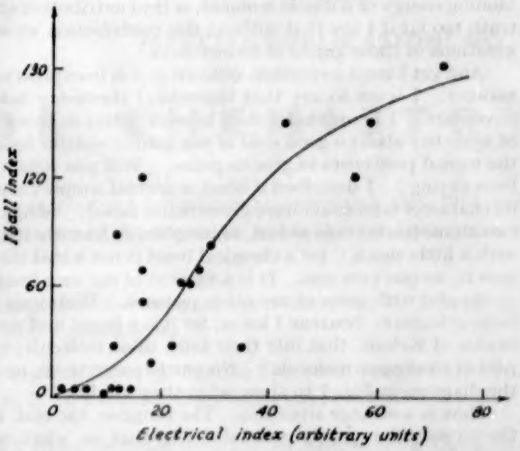


FIG. 19. *The variation of carcinogenic potency with electrical index of the* K*-region for some 24 different molecules. Each point represents a different molecule. The electrical index is purely theoretical, the carcinogenic activity, measured by the Iball index, is purely experimental.*



I have been speaking about past and present contributions of wave mechanics to our understanding of chemistry. But before I conclude I would like to say a little about possible future contributions. One conclusion at least seems quite clear : a very large part of that field which we call biological phenomena must eventually swim into this net. I am not thinking just of the normal metabolic processes such as oxidation, but also of the more abnormal ones. A start has been made with drugs, relating the efficacy of a drug to the distribution of charge within it. But perhaps the best example so far concerns the carcinogenic power of various aromatic hydrocarbons. Some of these molecules are exceedingly effective in causing tumours either by injection under the skin or even painting on the surface of the skin, of animals such as mice and rabbits. A large class of such molecules can be recognised where, following some pioneer work of Schmidt and Swartholm, we attribute the potency to their possession of a *K*-region (Fig. 18). Molecules without a *K*-region are seldom effective, those with it often are active. The activity may usually be increased by a methyl substitution at the periphery of the molecule : it may be reduced by replacement of a CH group by a N atom. Now the electrical properties of the *K*-region may be calculated, as described earlier in this lecture. It turns out, thanks to work by Mme. Pullman and Dr. Daudel in France, and Greenwood in England, that an " electrical index " can be devised. This index depends in a simple way upon the charges and bond orders in the *K*-region. If the index for a given molecule exceeds a certain threshold value, the molecule

is likely to be carcinogenic: otherwise it is not. Fig. 19 shows how the carcinogenic potency, measured in terms of the Iball index, varies with the electrical index for the *K*-region. There is a fair amount of "scatter" among the points. To some extent this is almost inevitable in work of this kind, where different animals must be expected to react differently to similar doses of the carcinogen. But few people would be tempted to deny that some sort of correlation exists. This does not "explain" the mechanism, nor does it give us control, of cancer. But it is one step on the way, a pointer to what will eventually become yet one more field in which wave mechanics plays its part, along with other types of experience, in a fuller understanding of Nature's mysteries.

Conclusion.—And now I have finished with my illustrations: they are all particular, and they are only a tiny gleaning from that larger harvest which has been gathered in these last 25 years. What are we to make of them? I believe that one characteristic shows most clearly of all. You must surely have been struck by the way in which, all along, modern wave mechanics has taken up ideas of the past, and refurbished them. How astonishingly fruitful have been those semi-formulated concepts of the classical chemists: and how necessary, in a sense, it has been for wave mechanics to give flesh and blood to the spirit which it has inherited. Think of the great names among the past that have come alive again in my short story—Mendeleef, Kekulé, Bayer, Werner, Thiele. Think of more modern ones—Ingold, Robinson, G. N. Lewis. At every turn we have seen how wave mechanics has taken their work and has added to it the quality of a deeper understanding. That of course is always how science proceeds, building the past into the present and enriching it thereby. We do see more deeply now into the meaning of our subject—what is really happening in chemistry. That, and not the calculation of a binding energy or a dipole moment, is the contribution of wave mechanics. Shall I be stretching truth too far if I say that without this contribution we should never have really appreciated the greatness of those giants of former days?

And yet I must go further, difficult as it is to express what I feel in any succinct and convincing manner. I want to say that theoretical chemistry holds within itself the stuff of intellectual adventure. I know that I shall be saying this in face of certain criticisms. For there is an air of unreality about a good deal of our subject matter today. And it does not require our friends the logical positivists to give us pause. Will you reflect a moment on some of the things I have been saying? I described a bond, a normal simple chemical bond; and I gave many details of its character (and could have given many more). Sometimes it seems to me that a bond between two atoms has become so real, so tangible, so friendly that I can almost see it. And then I awake with a little shock: for a chemical bond is not a real thing: it does not exist: no-one has ever seen it, no-one ever can. It is a figment of our own imagination.

So also with some of my other pictures. Hydrogen I know, for it is a gas and we keep it in large cylinders; benzene I know, for it is a liquid and we keep it in bottles. But what are these snakes of Kekulé, that bite their tails, these molecular orbitals that sprawl over the conjugated part of an organic molecule? No-one has seen them, no-one ever will, even though I have drawn the diagram in Fig. 7 to show what they are like!

Here is a strange situation. The tangible, the real, the solid, is explained by the intangible, the unreal, the purely mental. Yet that is what we chemists are always doing, wave-mechanically or otherwise. The great Darwin once gloomily described his mind as a "machine for grinding theories out of a mass of experimental facts." With us, as Mendeleef said, the facts are there and are being steadily accumulated day by day. Chemistry certainly includes all the chemical information and classification with which most school text-books are cluttered up. But it is more; for, because we are human, we are not satified with the facts alone; and so there is added to our science the sustained effort to correlate them and breathe into them the life of the imagination. It was one of our presidents, Sir Cyril Hinshelwood, who at our recent centenary commemorations, spoke of chemistry as "that most excellent child of intellect and art." And it was another chemist, Kekulé, who could say: "Let us learn to dream, gentlemen, and then perhaps we shall learn the truth." This is why we have chemical theories, and always have had; this is also why today's journey into the land of wave mechanics is no dull pedant's travel. It is the very stuff of intellectual adventure, in which creative ideas take shape and then illuminate both past and present with a new glory. For some of us, who have come more directly under the spell of the wave equation, it has satisfied us, so that even our long vigil in front of the calculating machine is not altogether unfulfilling. If, in the words of the poet, we have "scorned delights, to live laborious days," as, I fear, many of us have, it is because we have come to feel something about chemistry to which wave mechanics can contribute, and without which chemistry itself would be incomplete.

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